Supplementary Material

Synthesis and Molecular Docking Studies of Alkoxy- and Imidazole-Substituted Xanthones as α-Amylase and α-Glucosidase Inhibitors

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Copies of ^{1}H and ^{13}C NMR, and HRMS spectra for compounds **3**-**12**

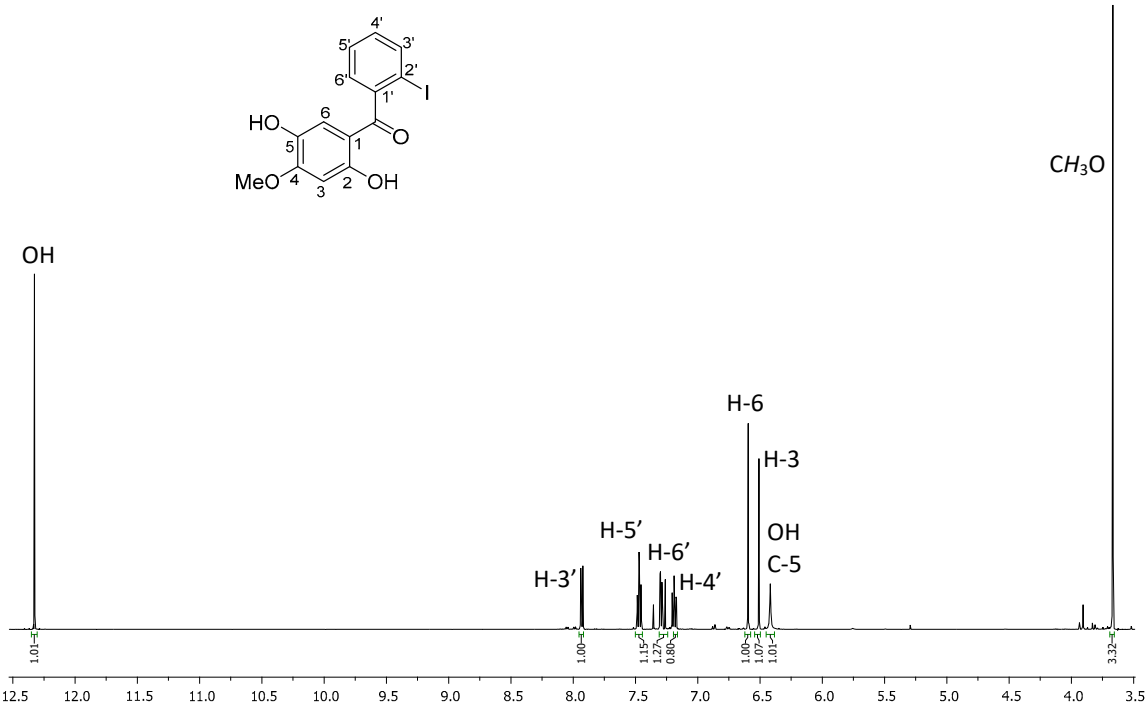


Figure S1. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **3a**.

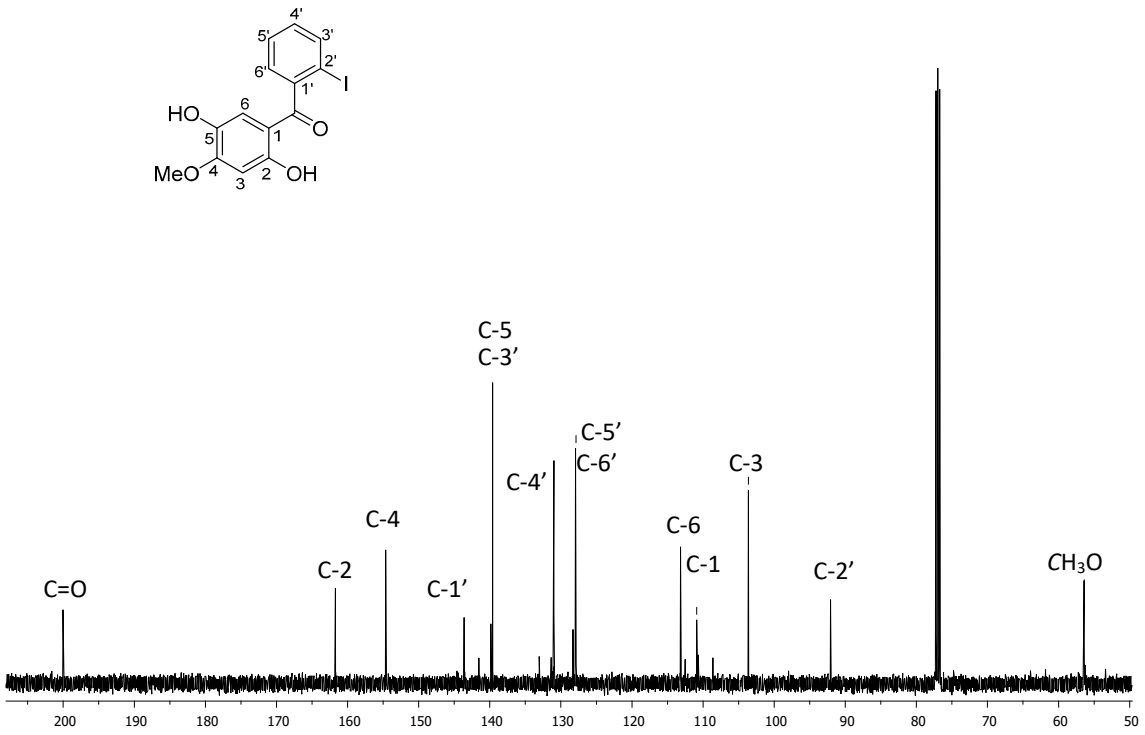


Figure S2. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **3a**.

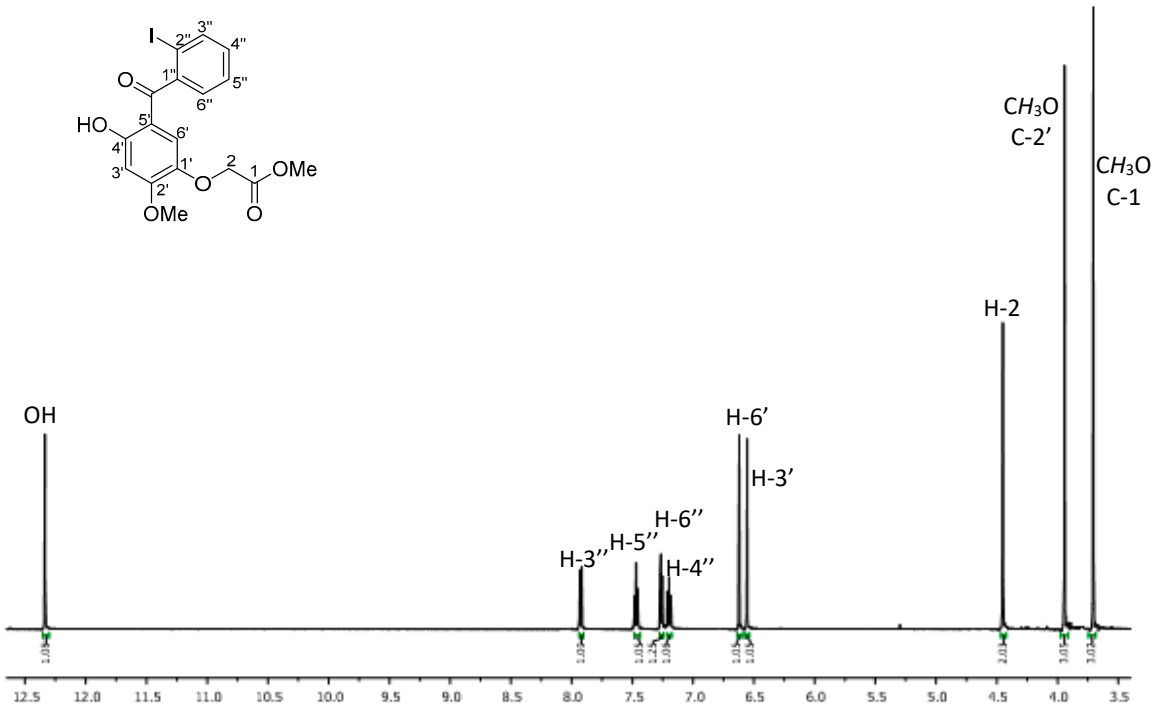


Figure S3. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **3b**.

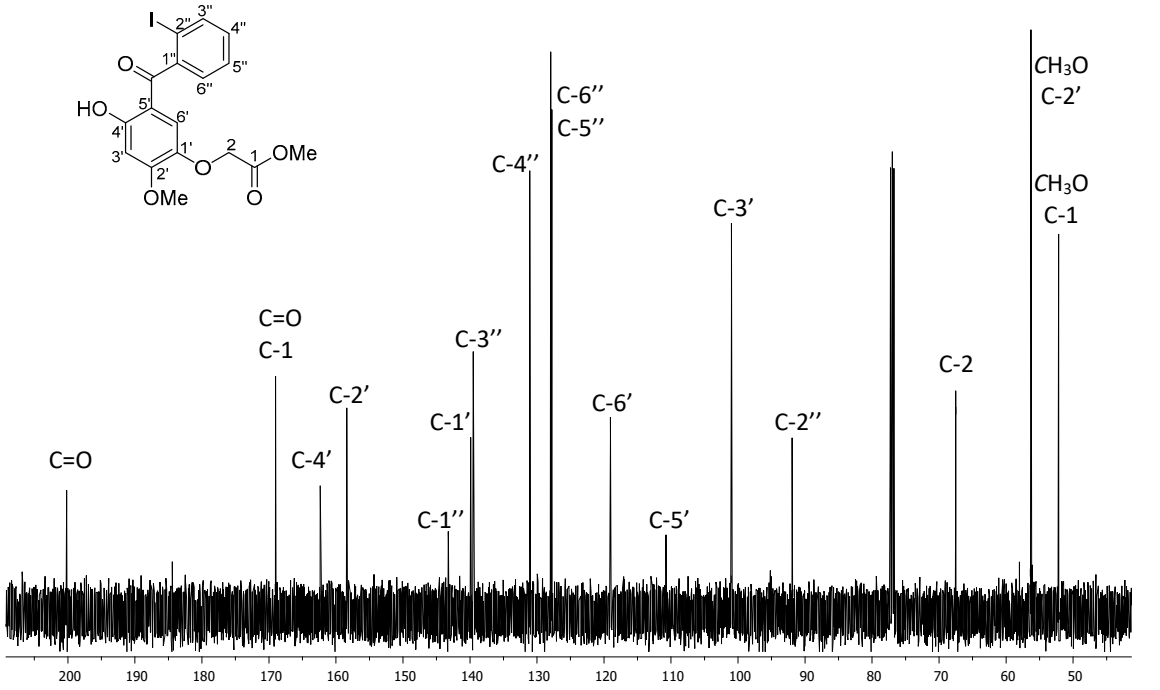


Figure S4. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **3b**.

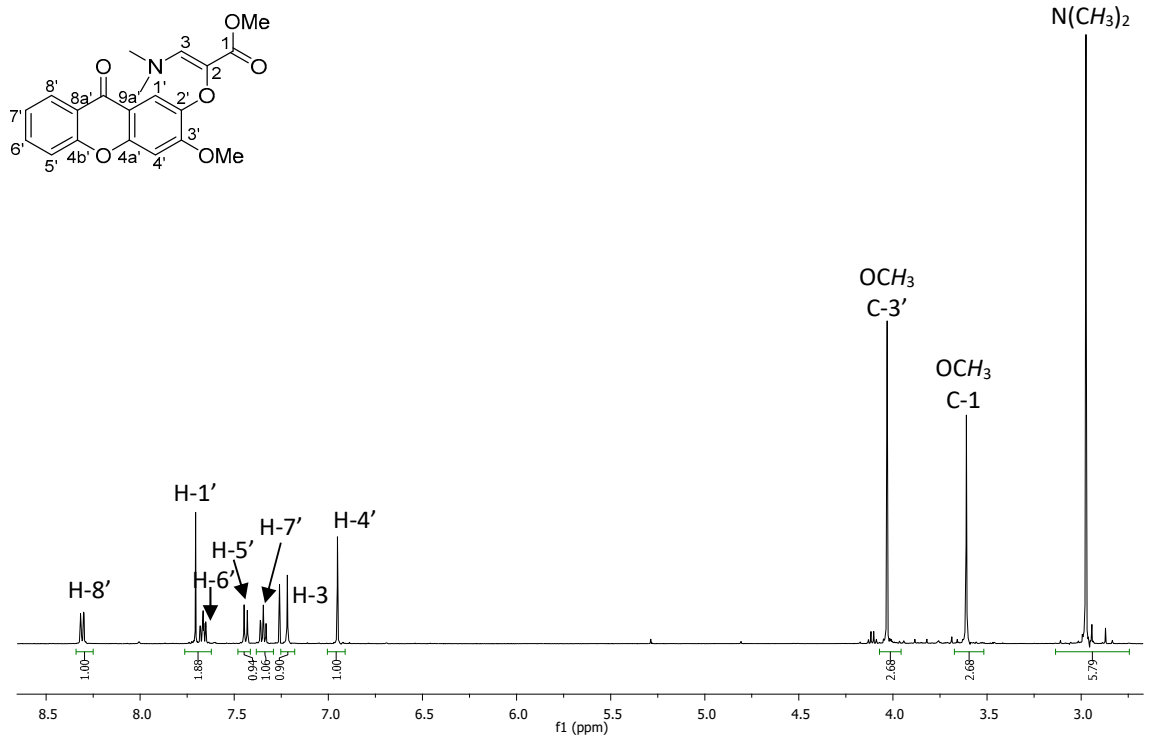


Figure S5. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **5**.

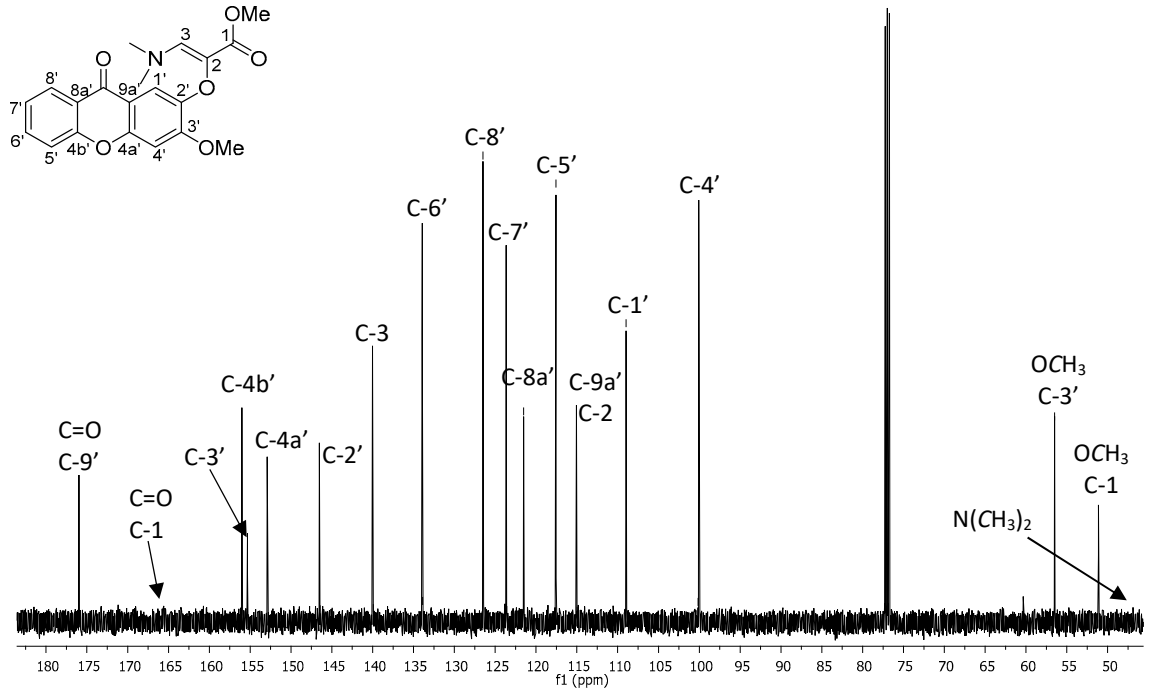
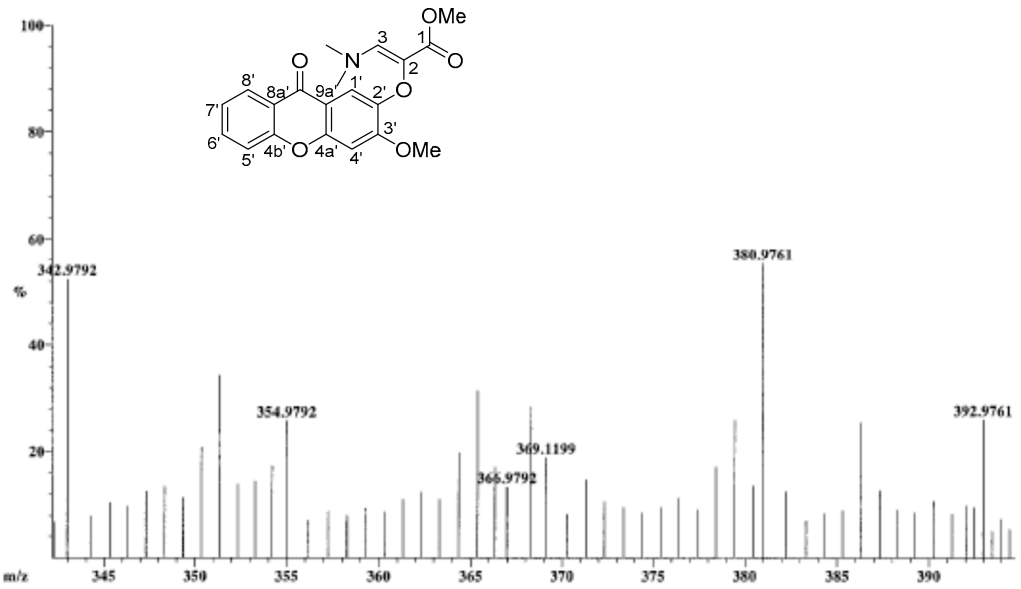


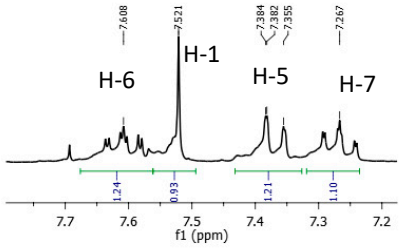
Figure S6. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **5**.

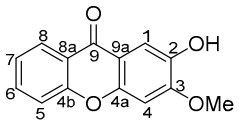


Selected Isotopes : $H_{0-19}C_{0-20}N_{0-1}O_{0-6}$ Error Limit : 5 ppm

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*
369.1199	19.0%	$C_{20}H_{19}NO_6$	369.1212	-3.6

Figure S7. HRMS (EI) spectra of compound **9a**.





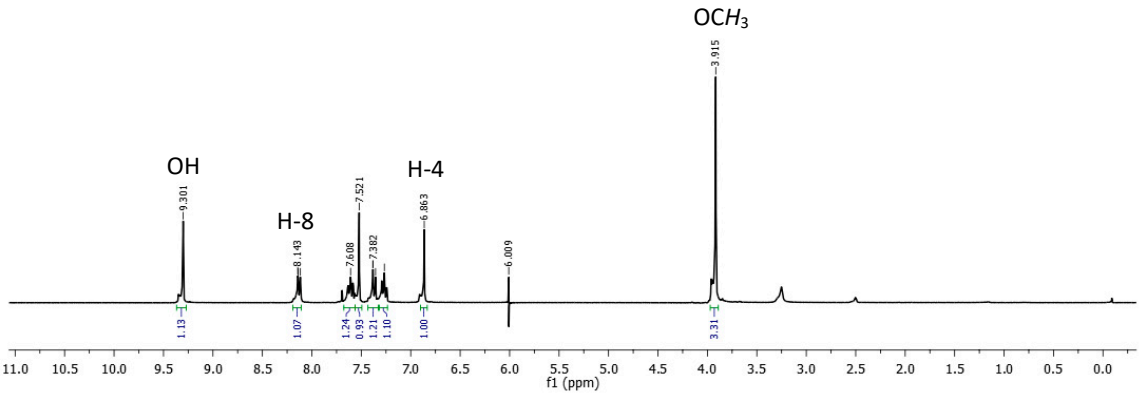


Figure S8. ^{1}H NMR (300 MHz, DMSO-d_6) spectrum of **1**.

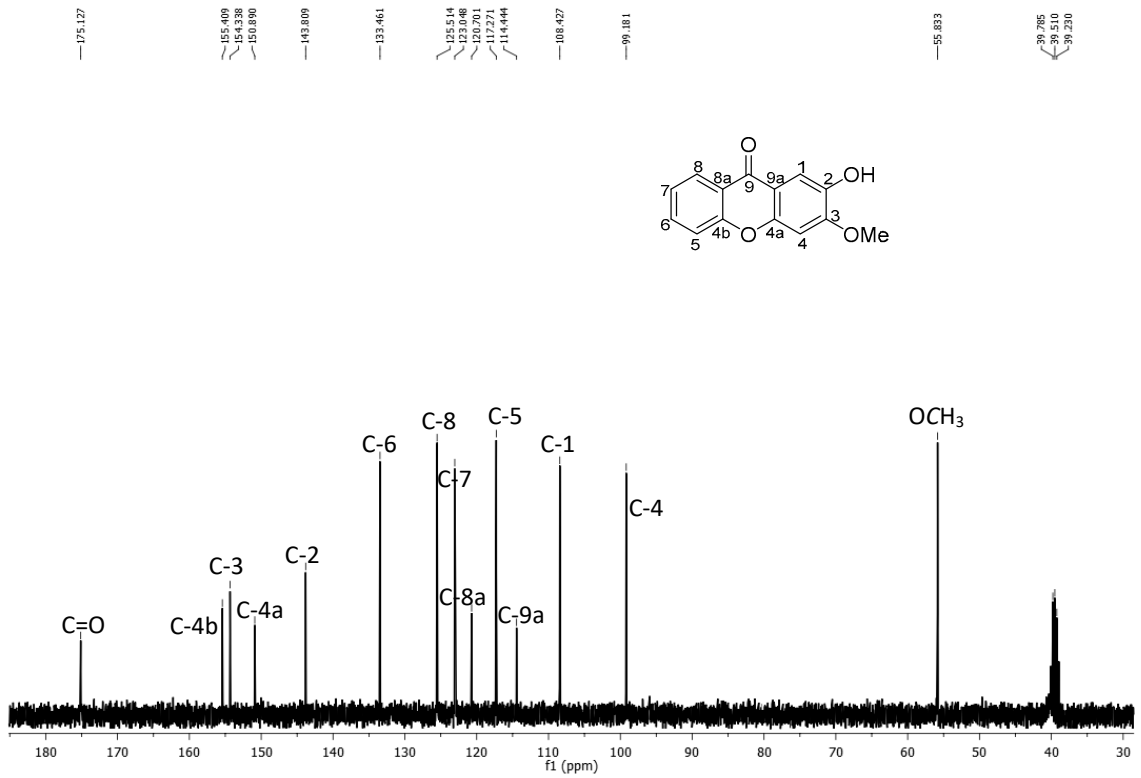


Figure S9. ^{13}C NMR (75 MHz, DMSO-d_6) spectrum of **1**.

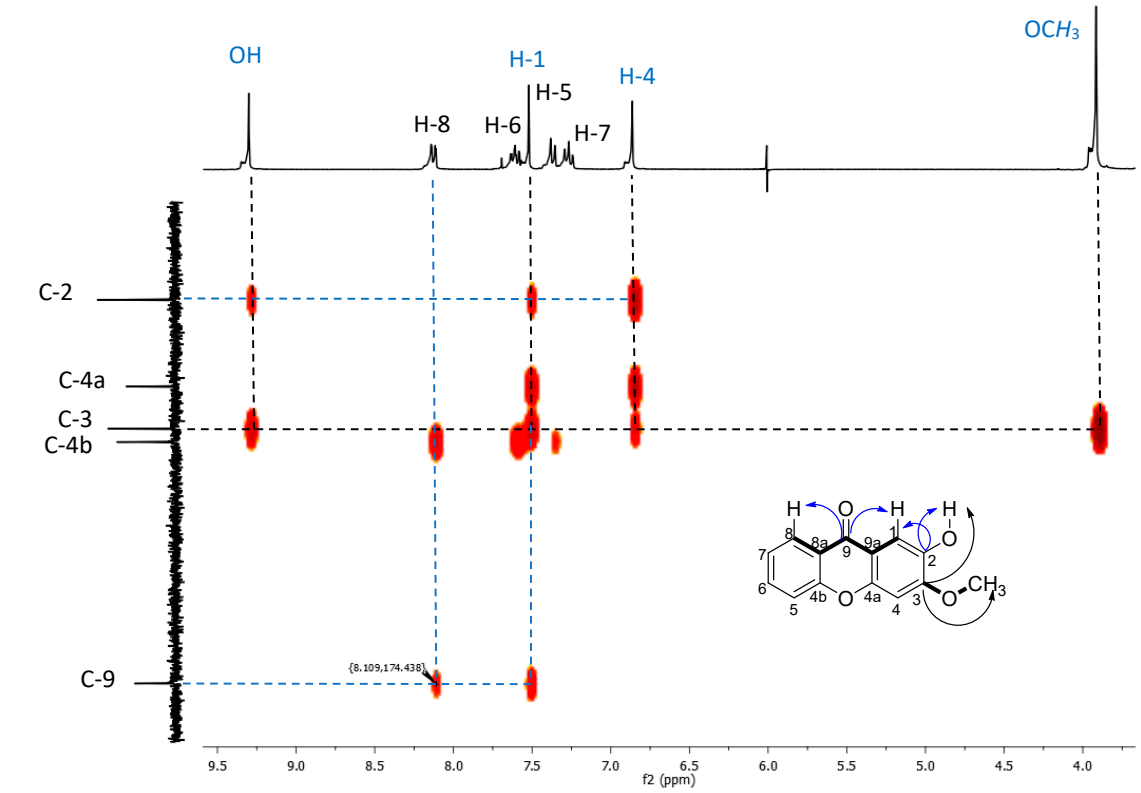


Figure S10. HMBC 2D NMR spectrum of **1**.

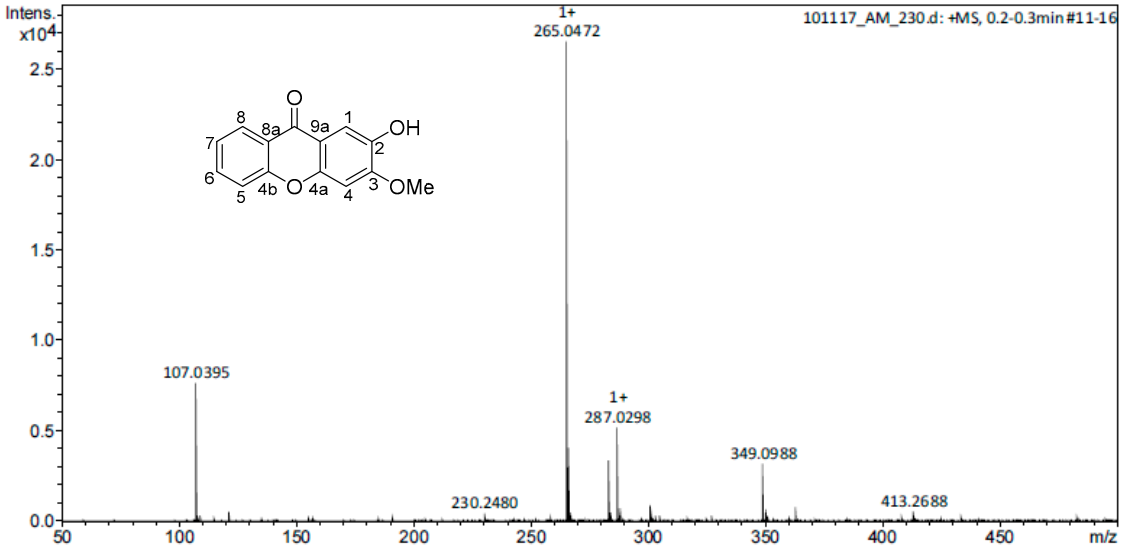


Figure S11. HRMS (ESI) spectra of compound **1**.

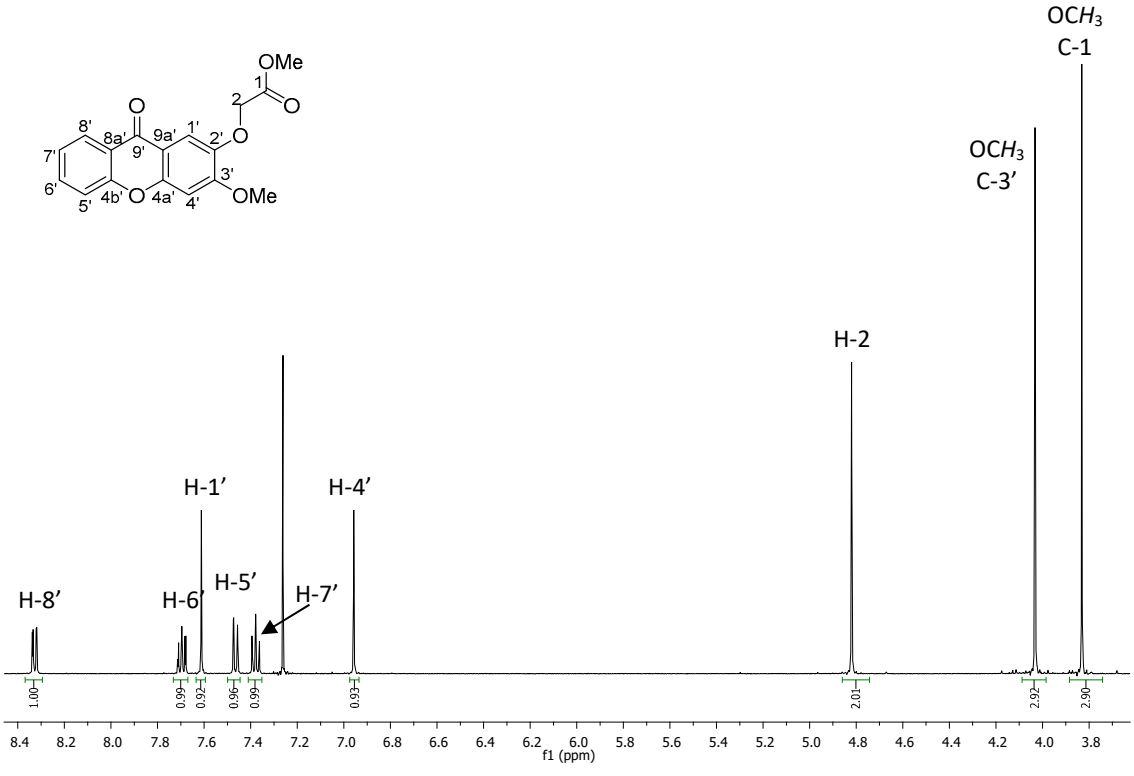


Figure S12. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **6a**.

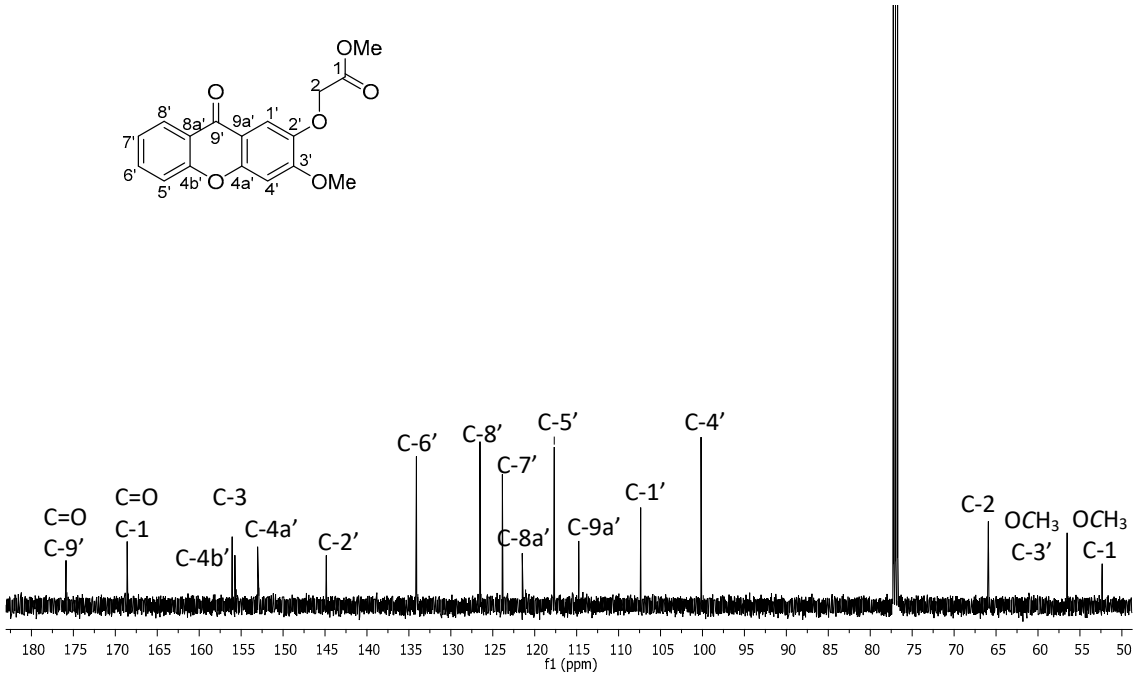
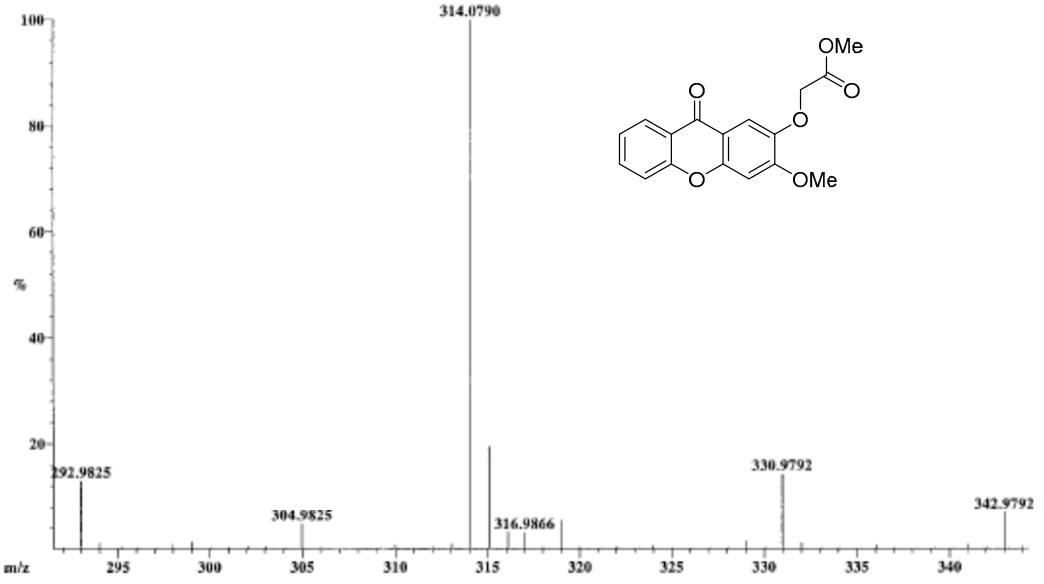


Figure S13. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **6a**.



Selected Isotopes : $H_{0-14}C_{0-17}O_{0-6}$ Error Limit : 5 ppm

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*
314.0790	100.0%	$C_{17}H_{14}O_6$	314.0790	-0.1

Figure S14. HRMS (EI) spectra of compound **6a**.

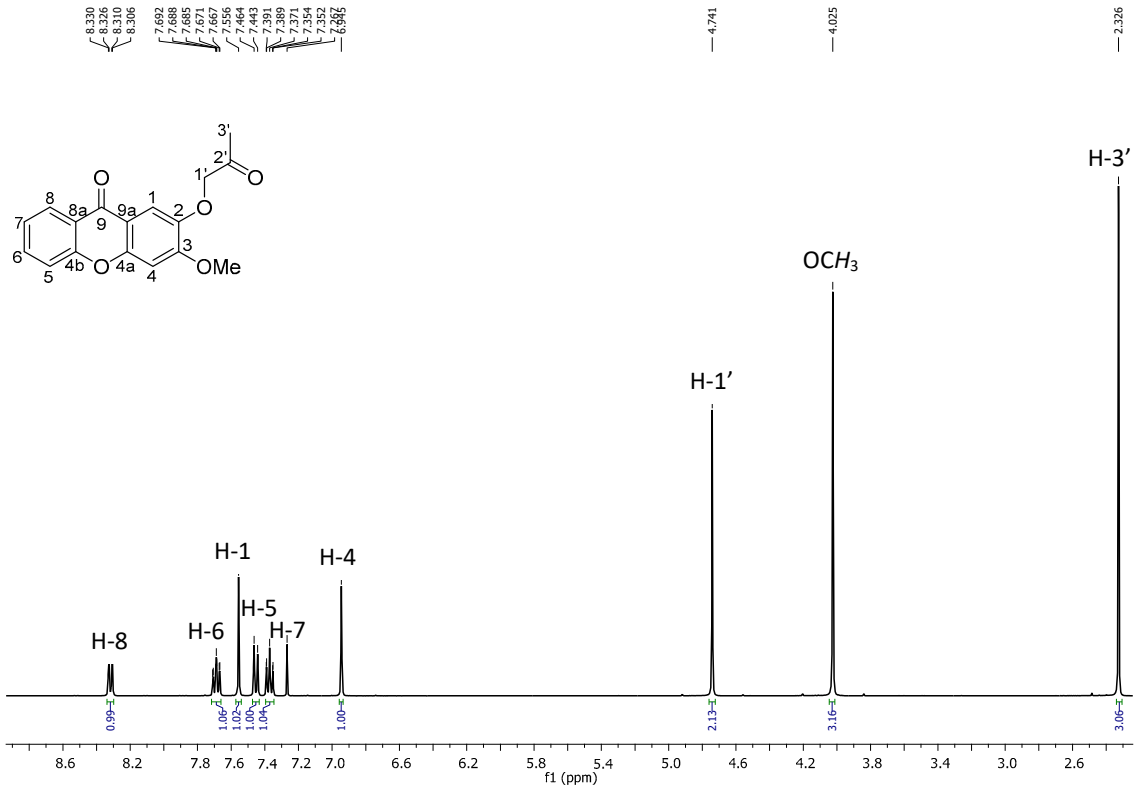


Figure S15. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **6b**.

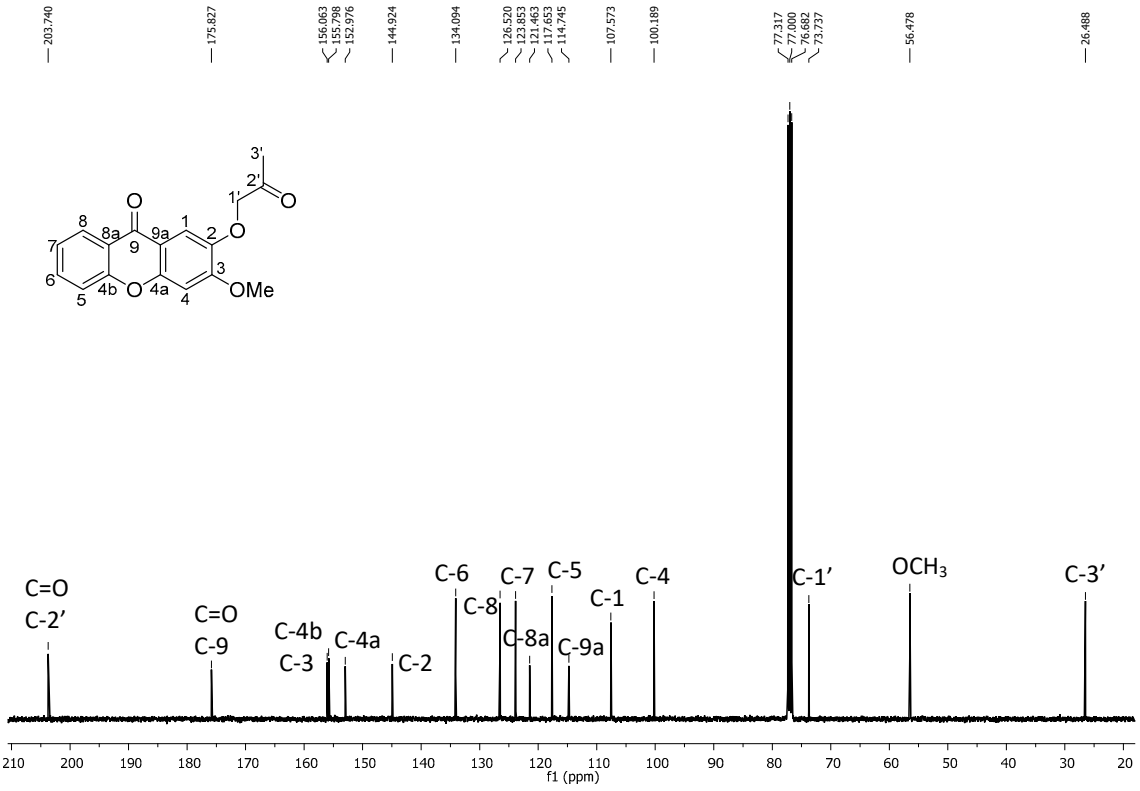


Figure S16. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **6b**.

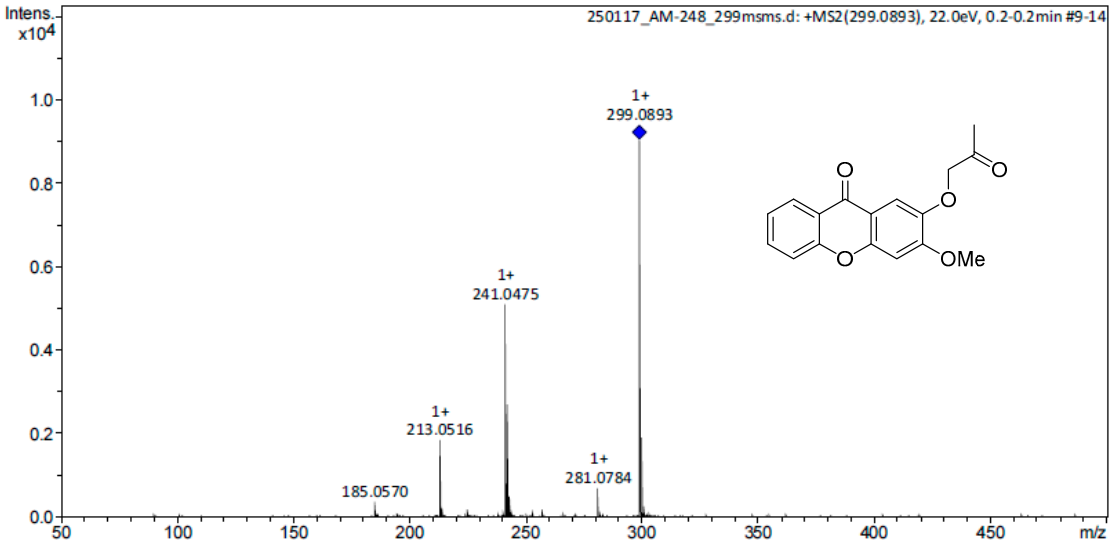


Figure S17. HRMS (ESI) spectra of compound **6b**.

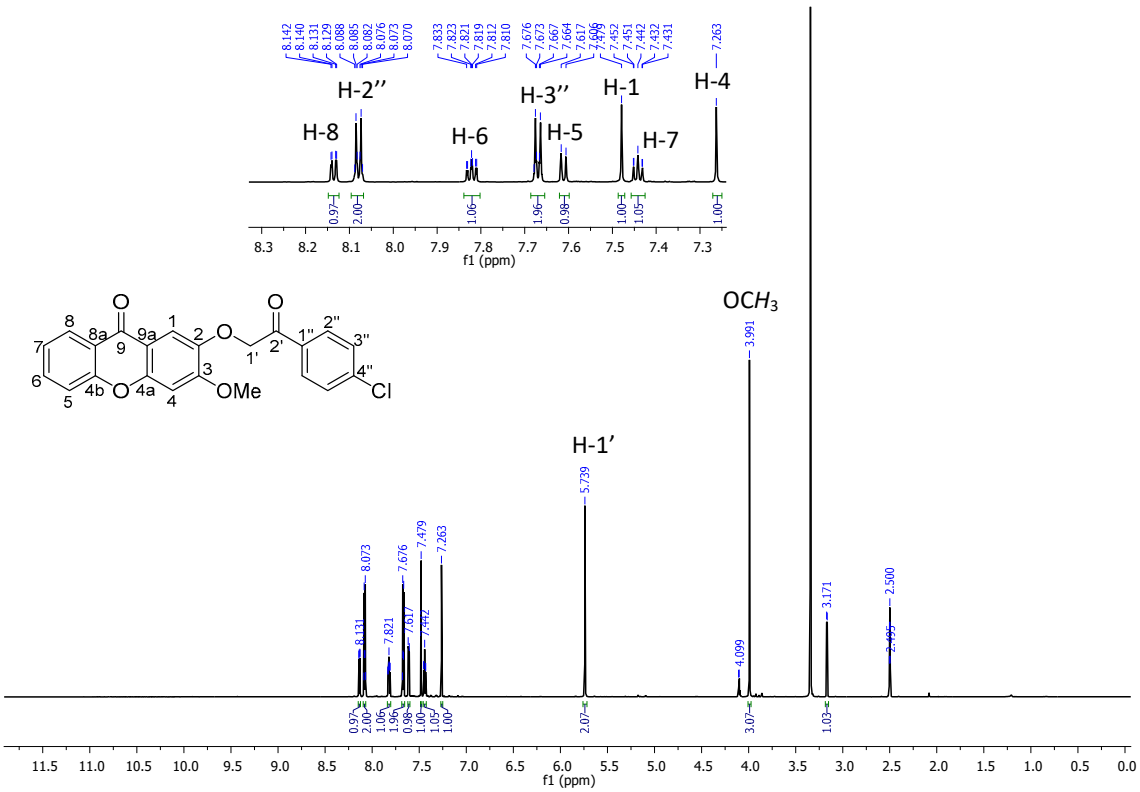


Figure S18. ^{1}H NMR (750 MHz, DMSO-d_6) spectrum of **6c**.

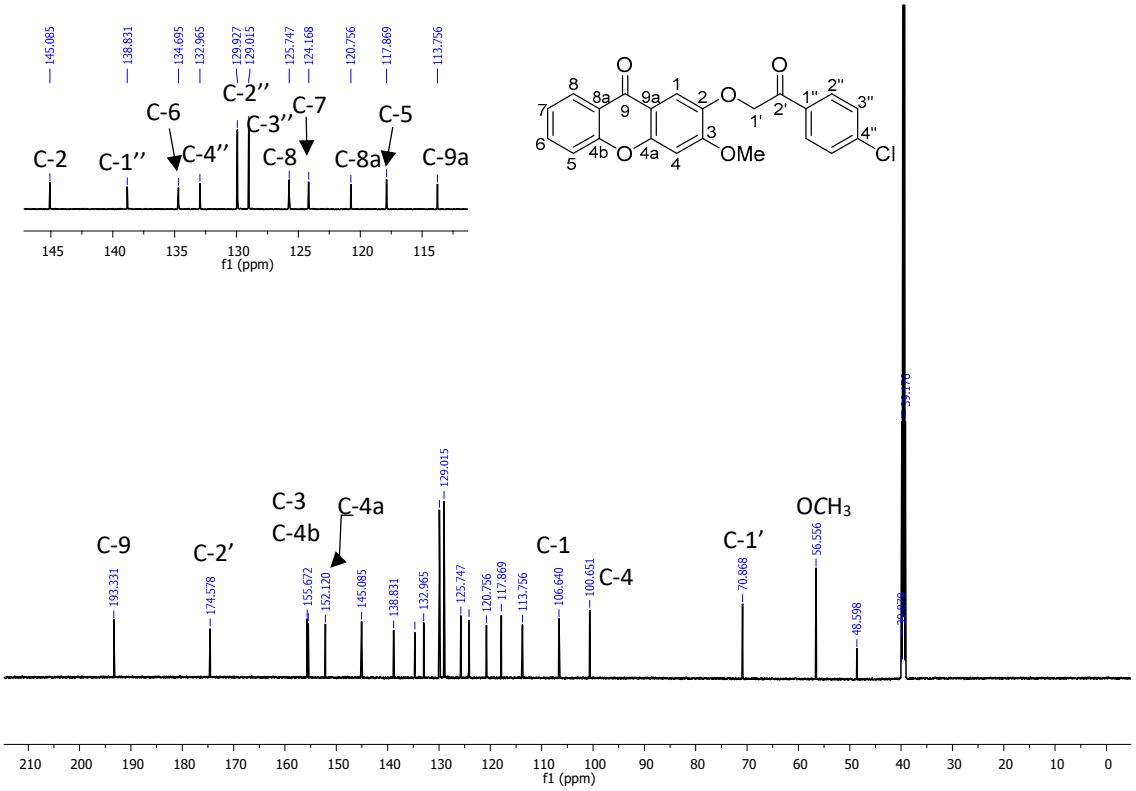
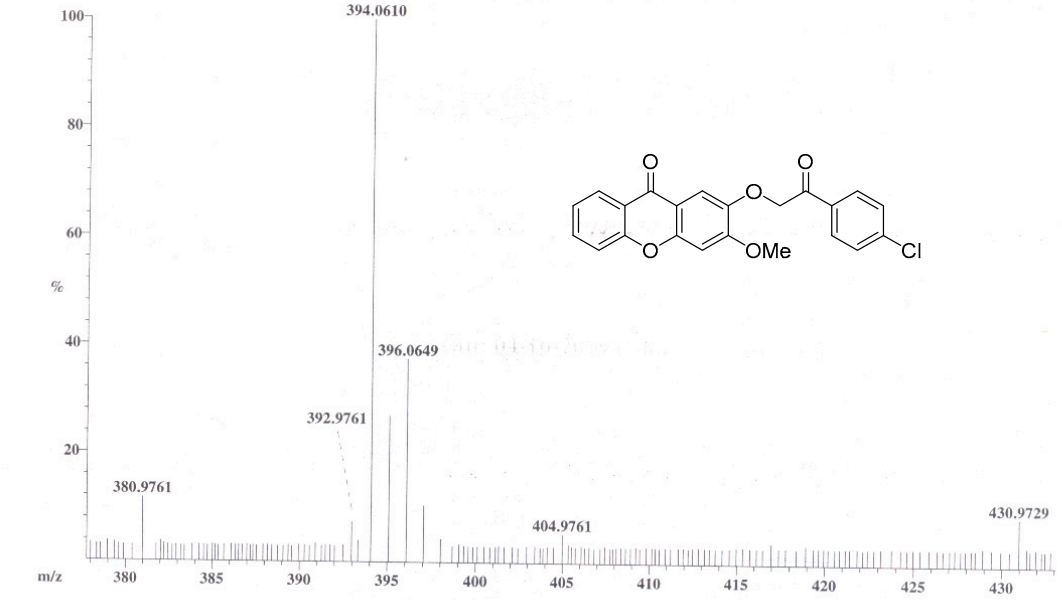


Figure S19. ^{13}C NMR (187.5 MHz, DMSO-d_6) spectrum of **6c**



Selected Isotopes : $H_{0-15}C_{0-22}O_{0-5}Cl_{0-1}$ Error Limit : 5 ppm

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*
394.0610	100.0%	$C_{22}H_{15}O_5Cl$	394.0608	0.5

Figure S20. HRMS (EI) spectra of compound **6c**.

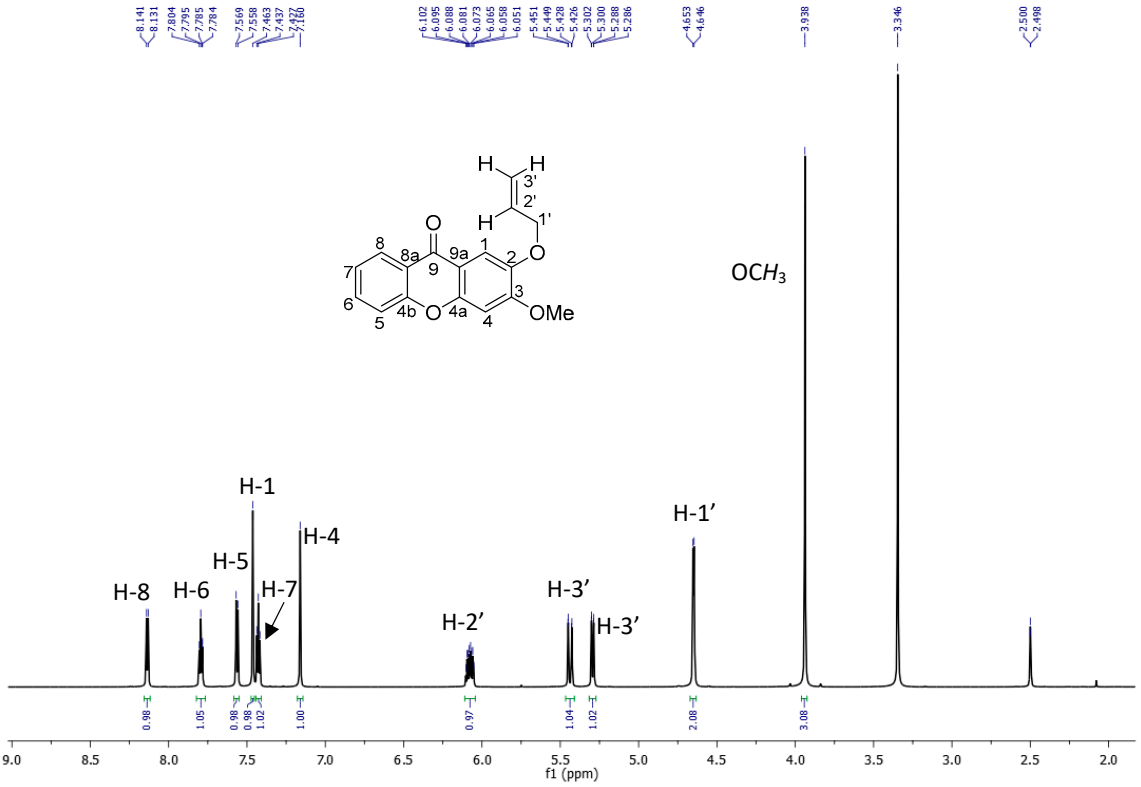


Figure S21. ^{1}H NMR (750 MHz, DMSO-d_6) spectrum of **6d**.

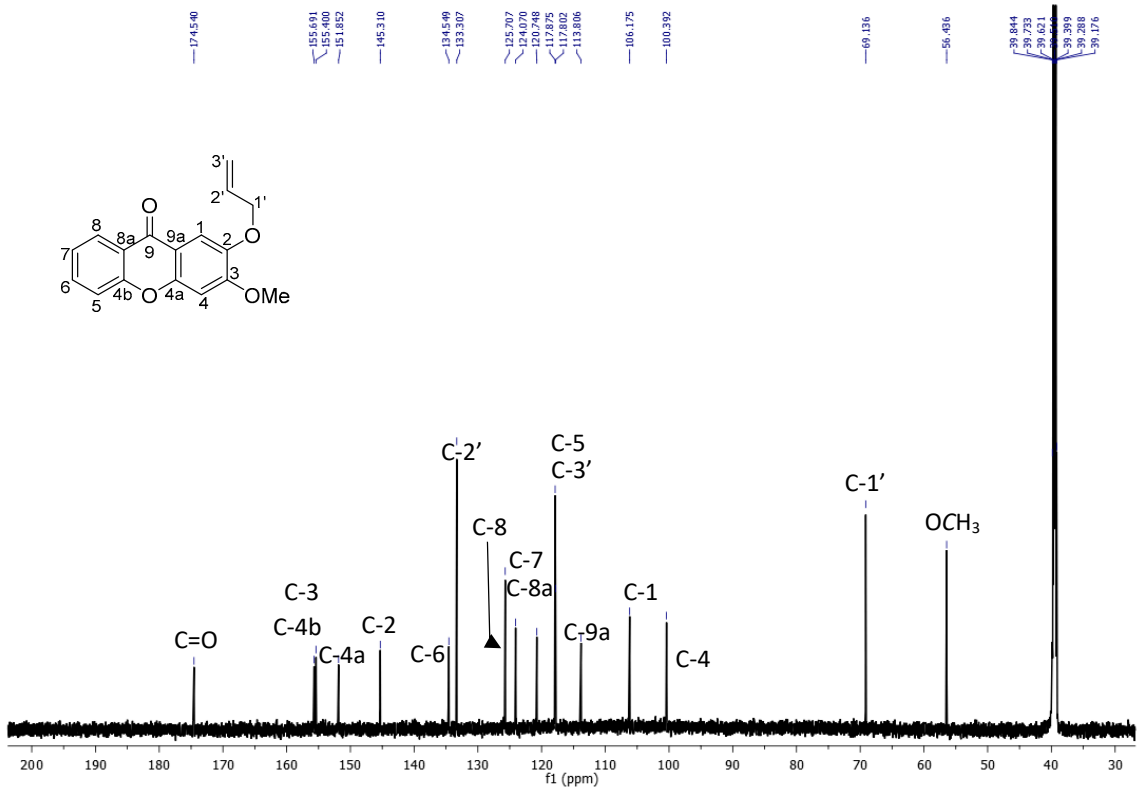


Figure S22. ^{13}C NMR (187.5 MHz, DMSO-d_6) spectrum of **6d**.

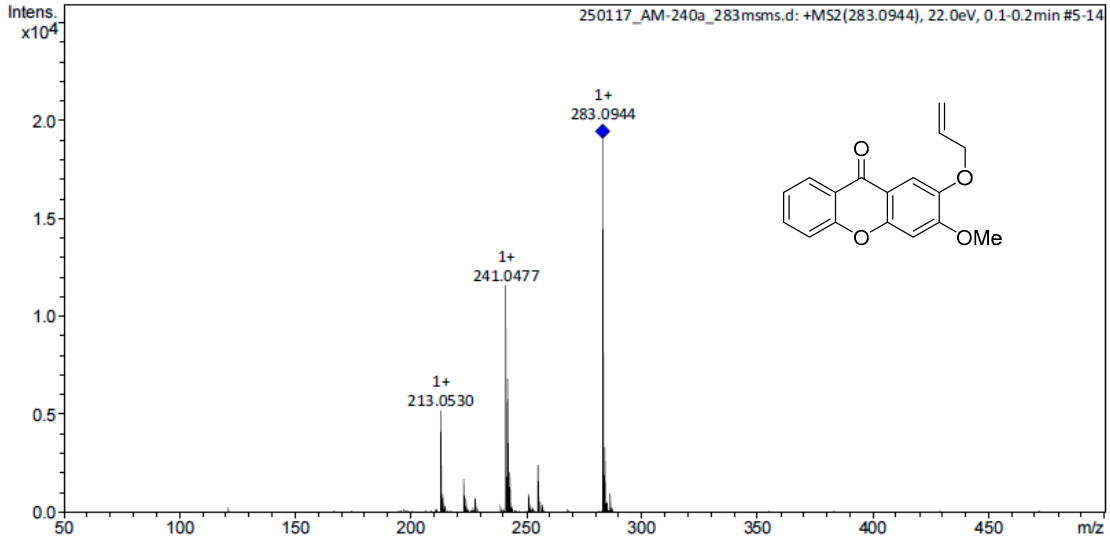


Figure S23. HRMS (ESI) spectra of compound **6d**.

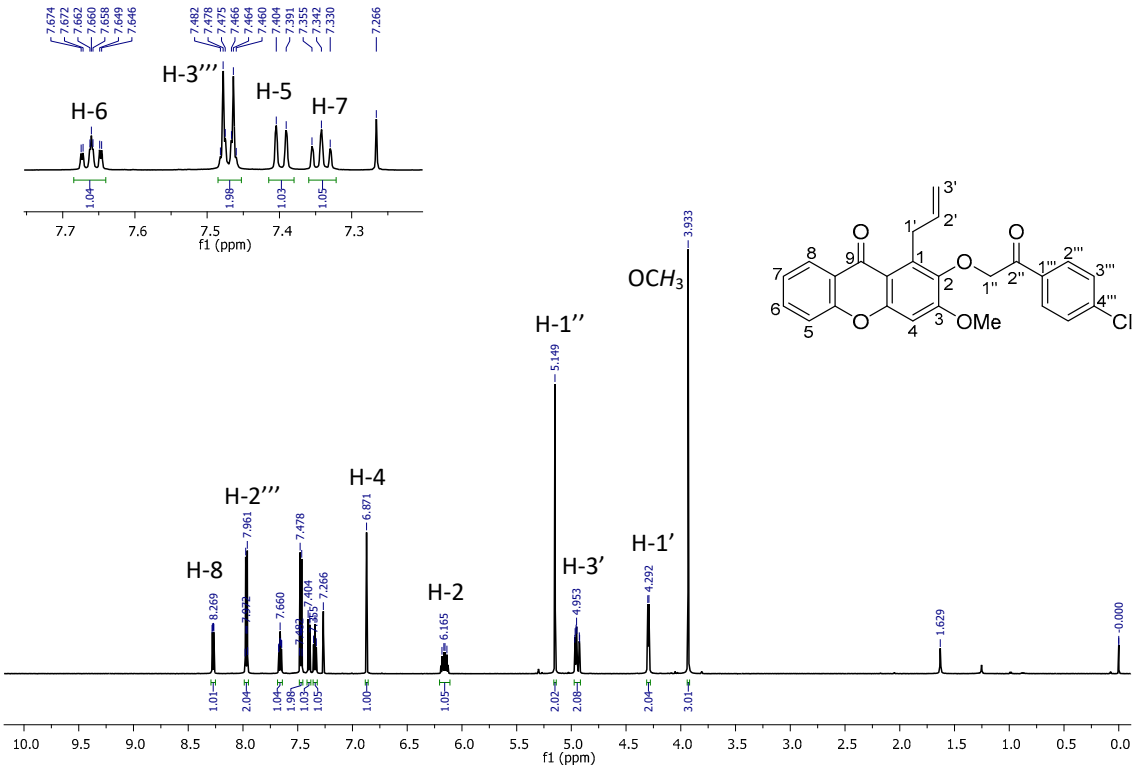


Figure S24. ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **6e**.

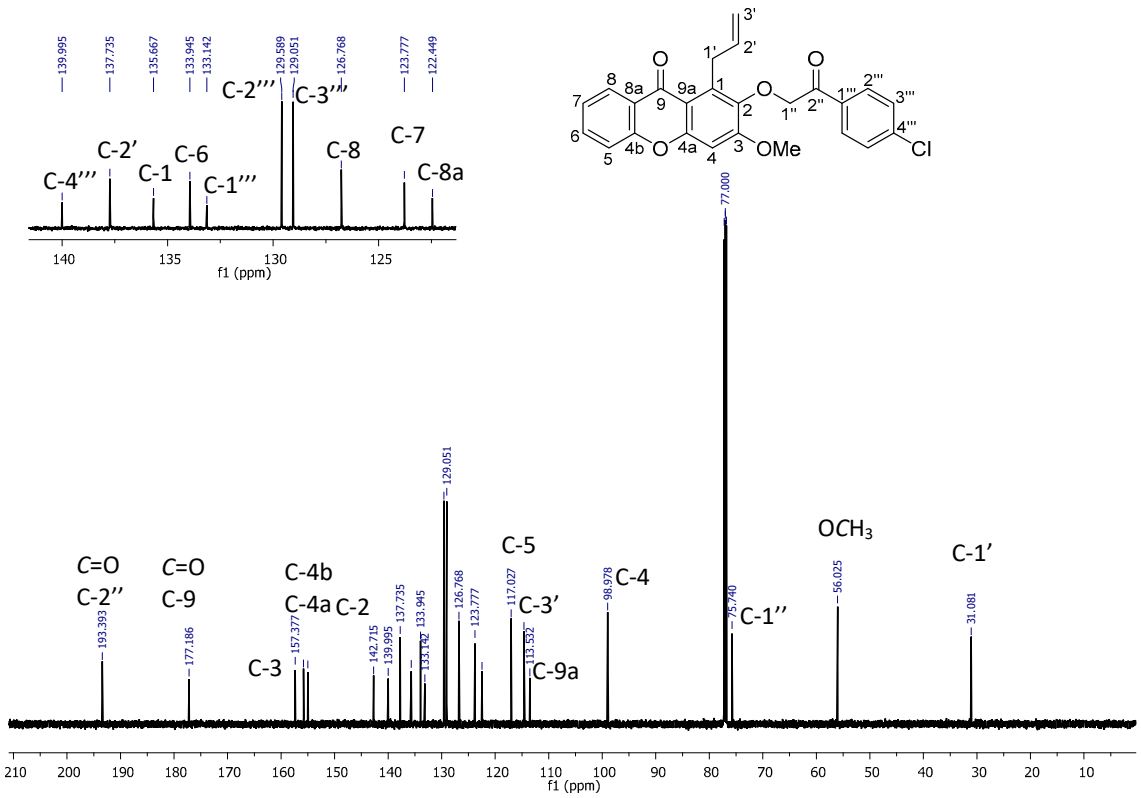
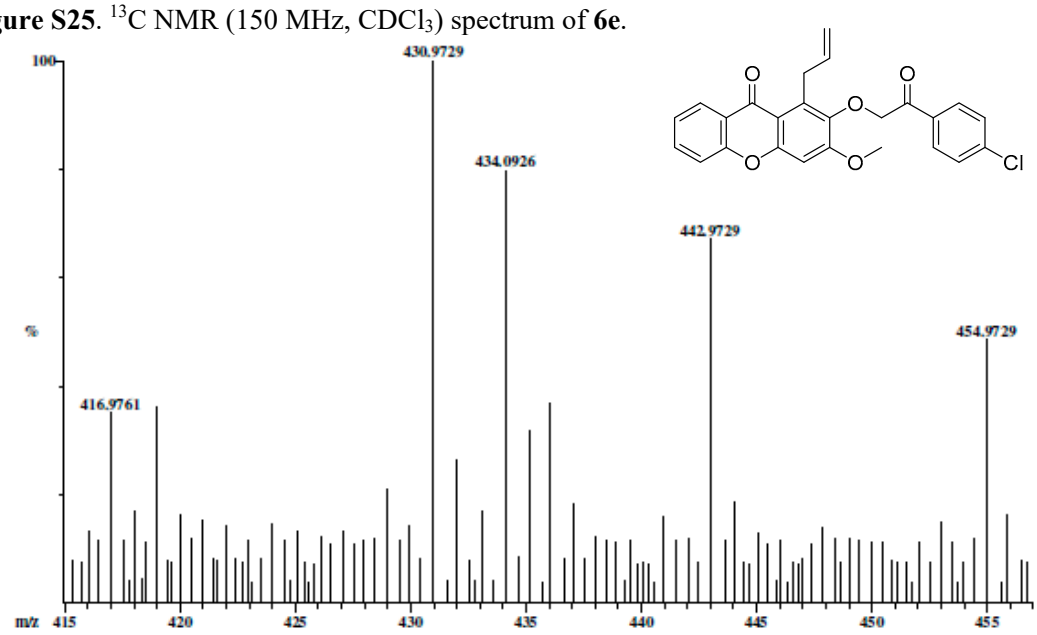


Figure S25. ^{13}C NMR (150 MHz, $CDCl_3$) spectrum of **6e**.



Selected Isotopes : $H_{0-19}C_{0-25}O_{0-5}Cl_{0-1}$ **Error Limit : 5 ppm**

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*
434.0926	**79.8%**	**$C_{25}H_{19}O_5Cl$**	**434.0921**	**1.2**

Figure S26. HRMS (EI) spectra of compound **6e**.

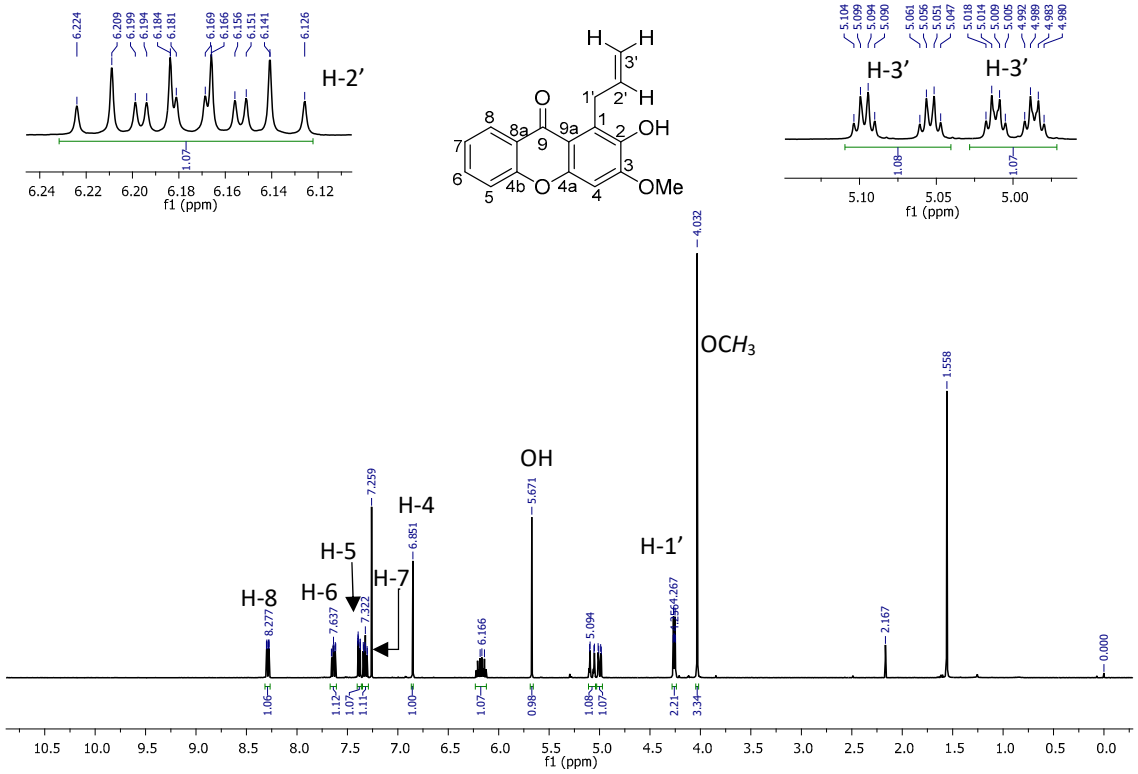


Figure S27. ^{1}H NMR (750 MHz, $CDCl_3$) spectrum of **7**.

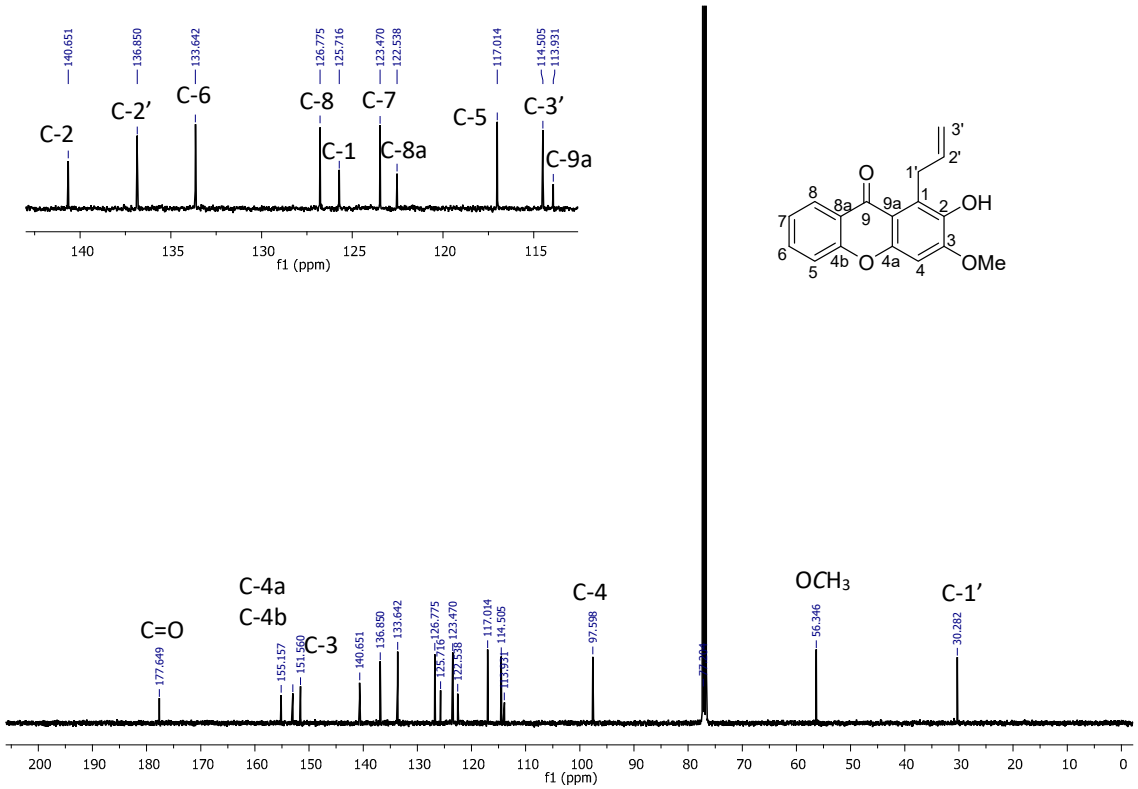


Figure S28. ^{13}C NMR (187.5 MHz, $CDCl_3$) spectrum of **7**.

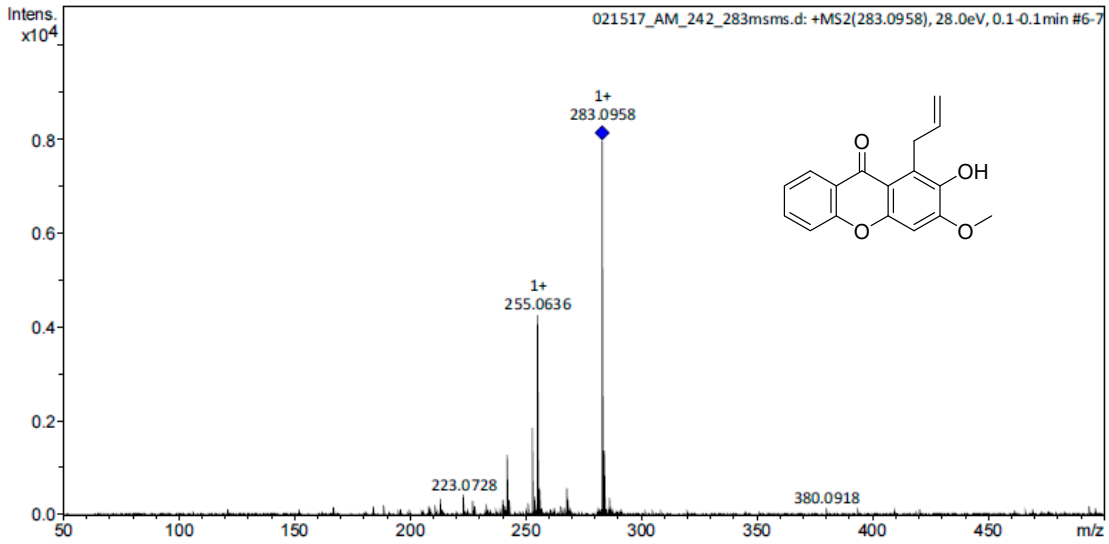


Figure S29. HRMS (ESI) spectra of compound **7**.

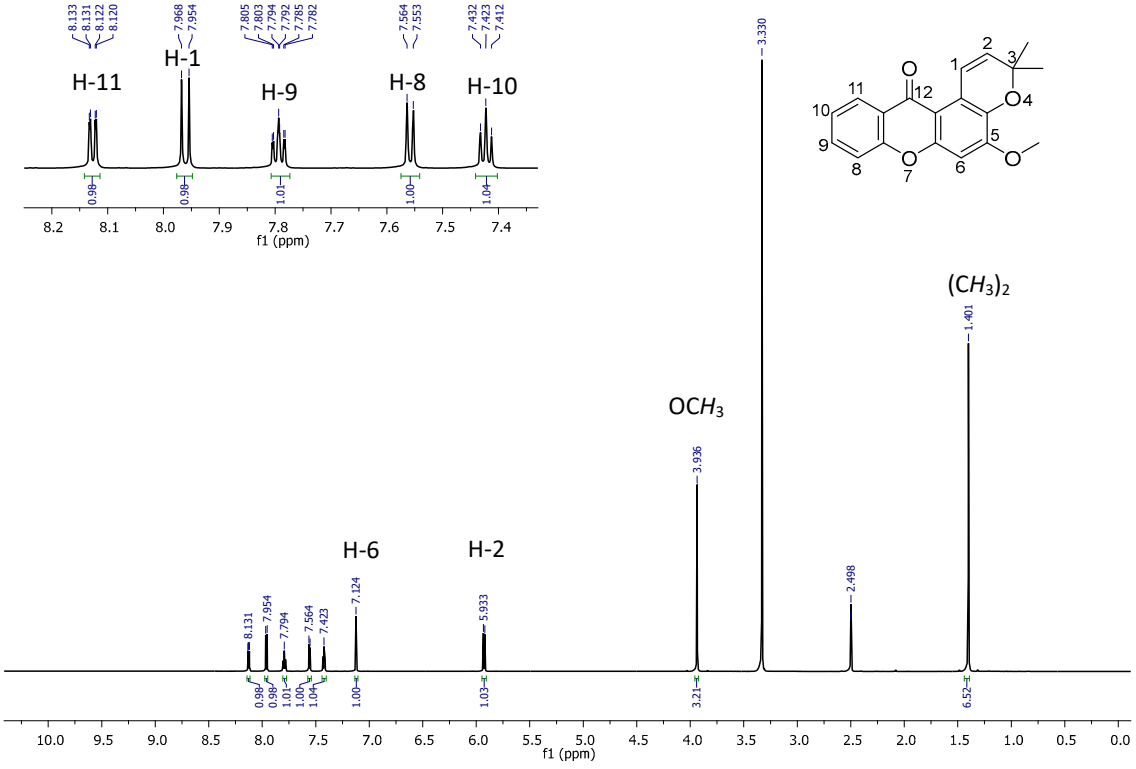


Figure 30 ^{1}H NMR (750 MHz, DMSO-d_6) spectrum of **8**.

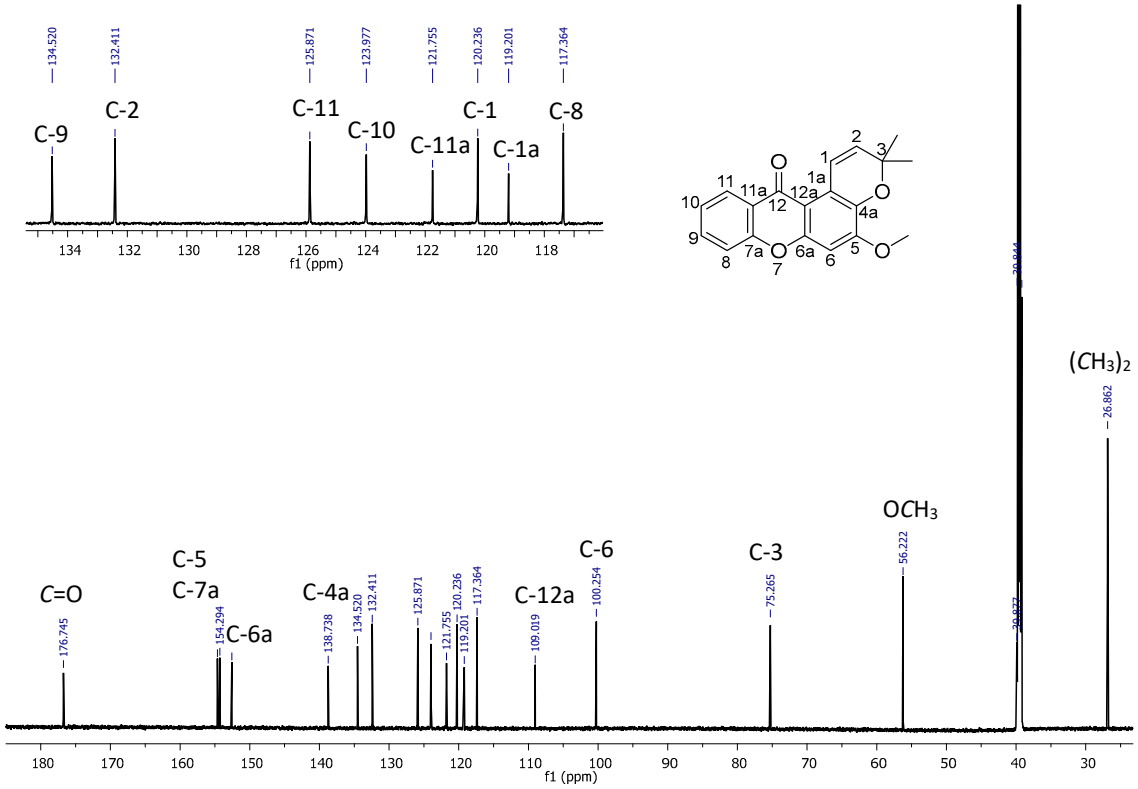
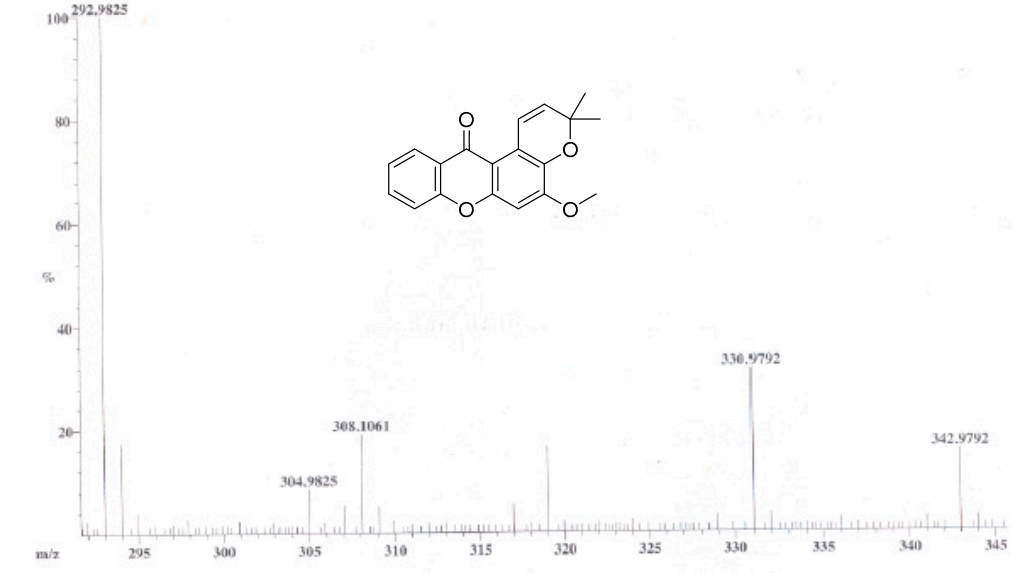


Figure S31. ^{13}C NMR (187.5 MHz, DMSO-d_6) spectrum of **8**.



Selected Isotopes : $H_{0\text{-}16}C_{0\text{-}19}O_{0\text{-}4}$ Error Limit : 5 ppm

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*
308.1061	19.0%	$C_{19}H_{16}O_4$	308.1049	4.0

Figure S32. HRMS (EI) spectra of compound **8**.

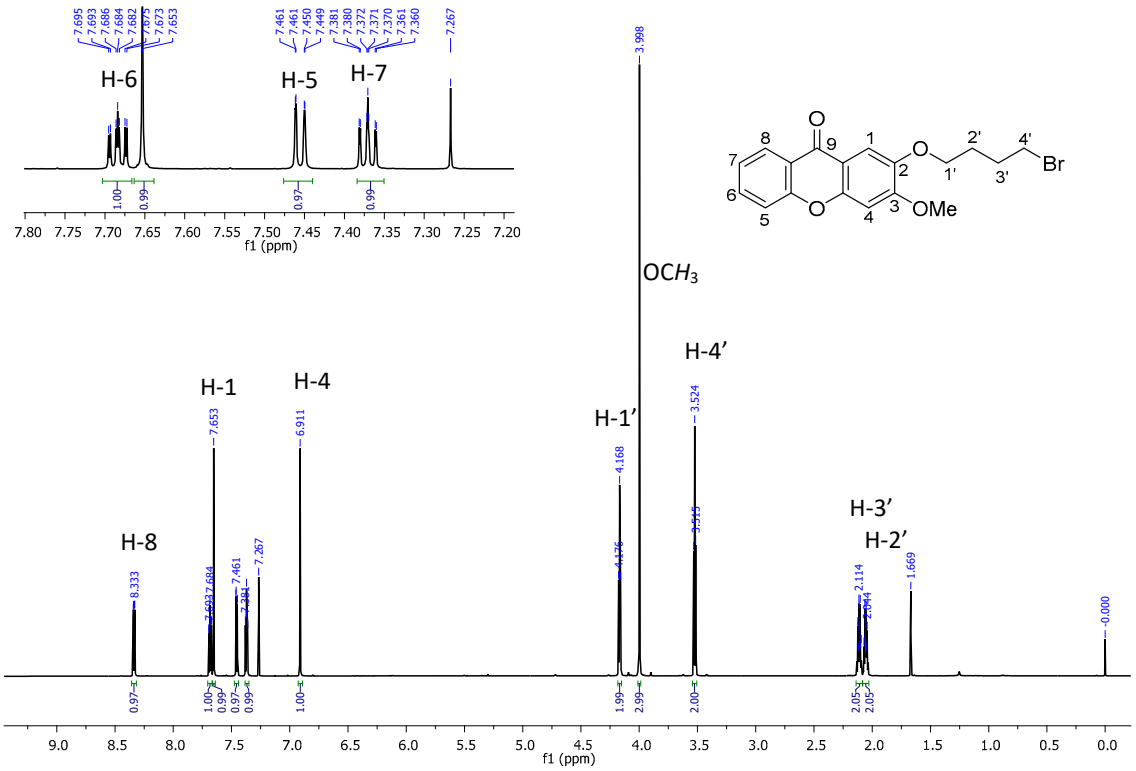


Figure S33. ^{1}H NMR (750 MHz, $CDCl_3$) spectrum of **9a**.

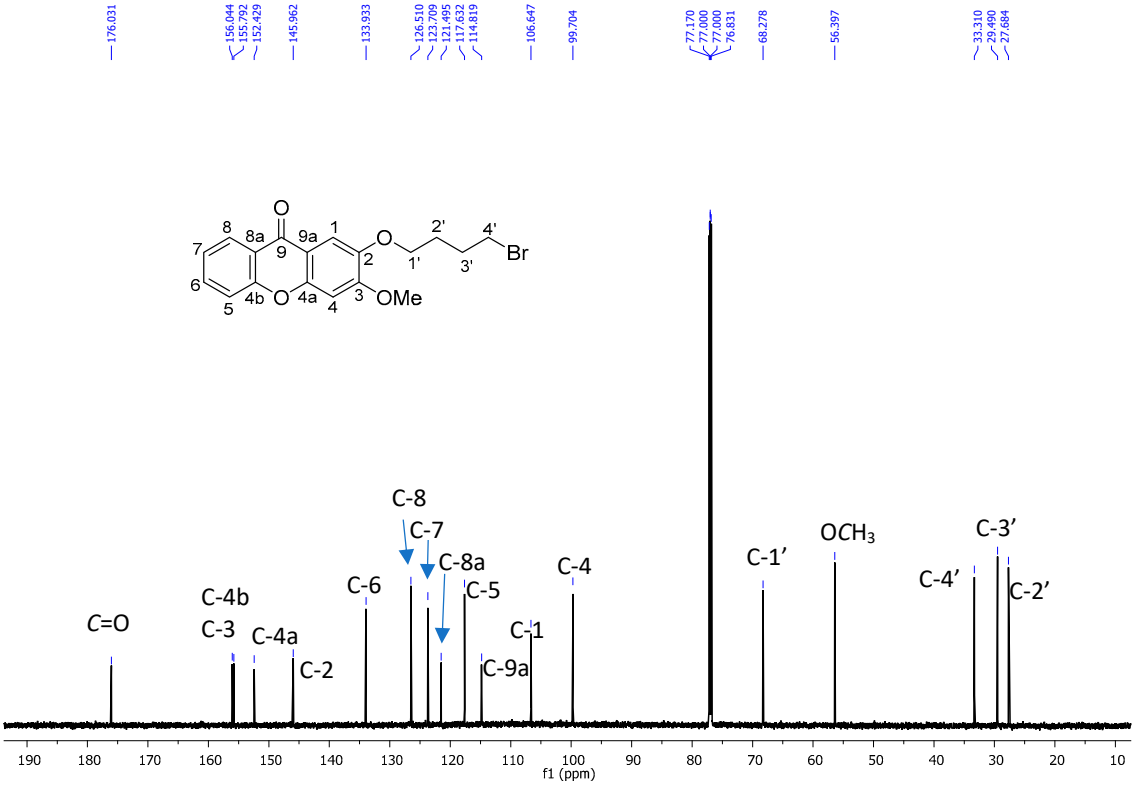
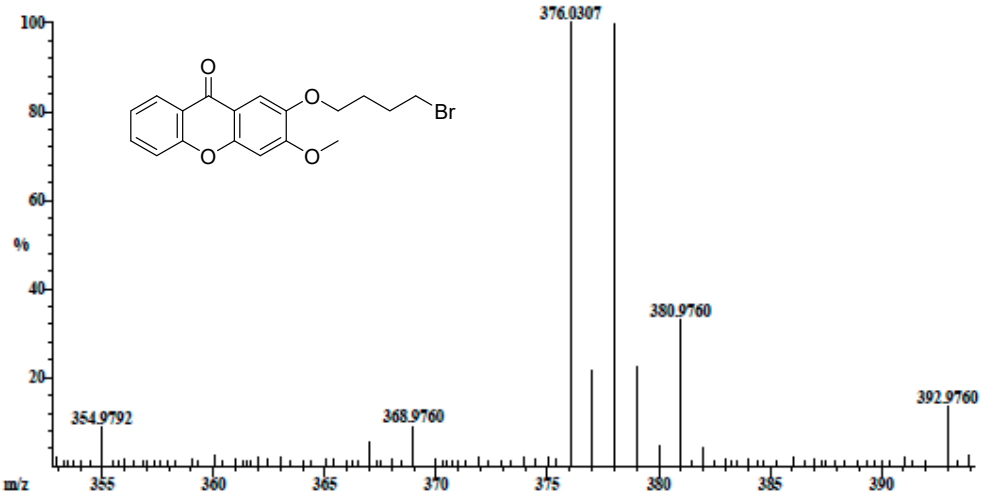


Figure S34. ^{13}C NMR (187.5 MHz, $CDCl_3$) spectrum of **9a**



Selected Isotopes : $H_{0-17}C_{0-18}O_{0-4}Br_{0-1}$ Error Limit : 5 ppm Unsaturation Limits : 0 to 50

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*	*Unsaturation*
376.0307	100.0%	$C_{18}H_{17}O_4Br$	376.0310	-0.8	10.0

Figure S35. HRMS (EI) spectra of compound **9a**.

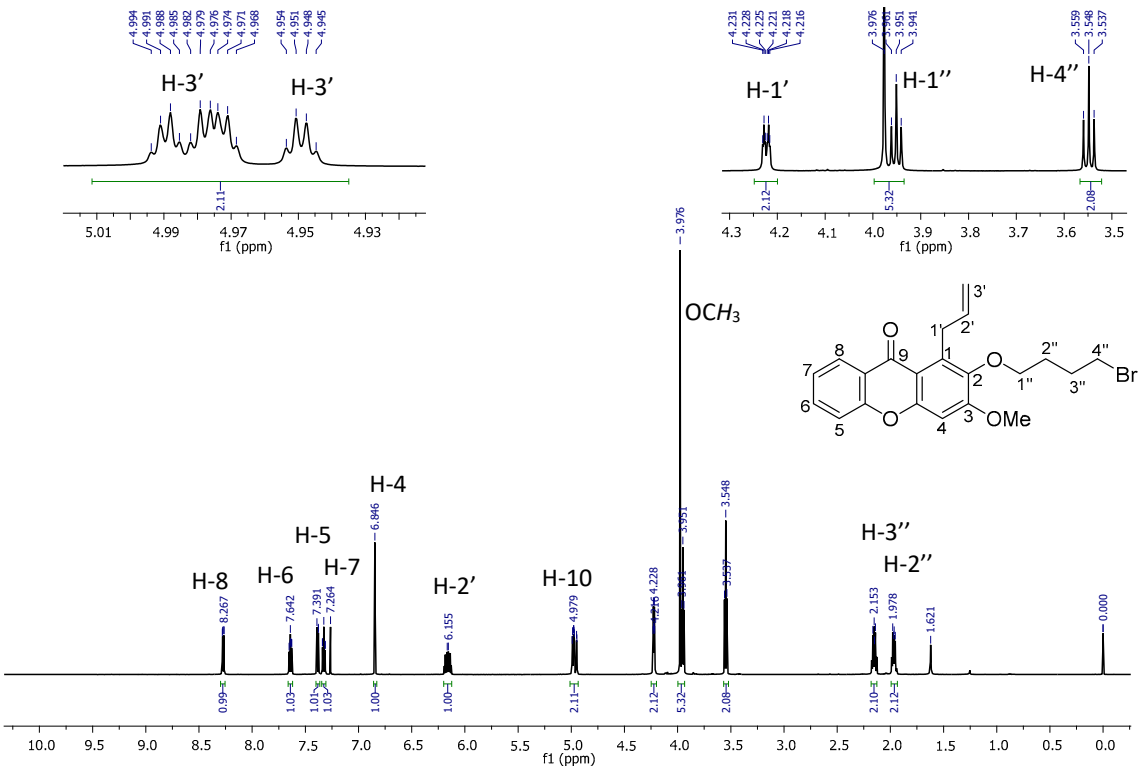


Figure S36. ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **9b**.

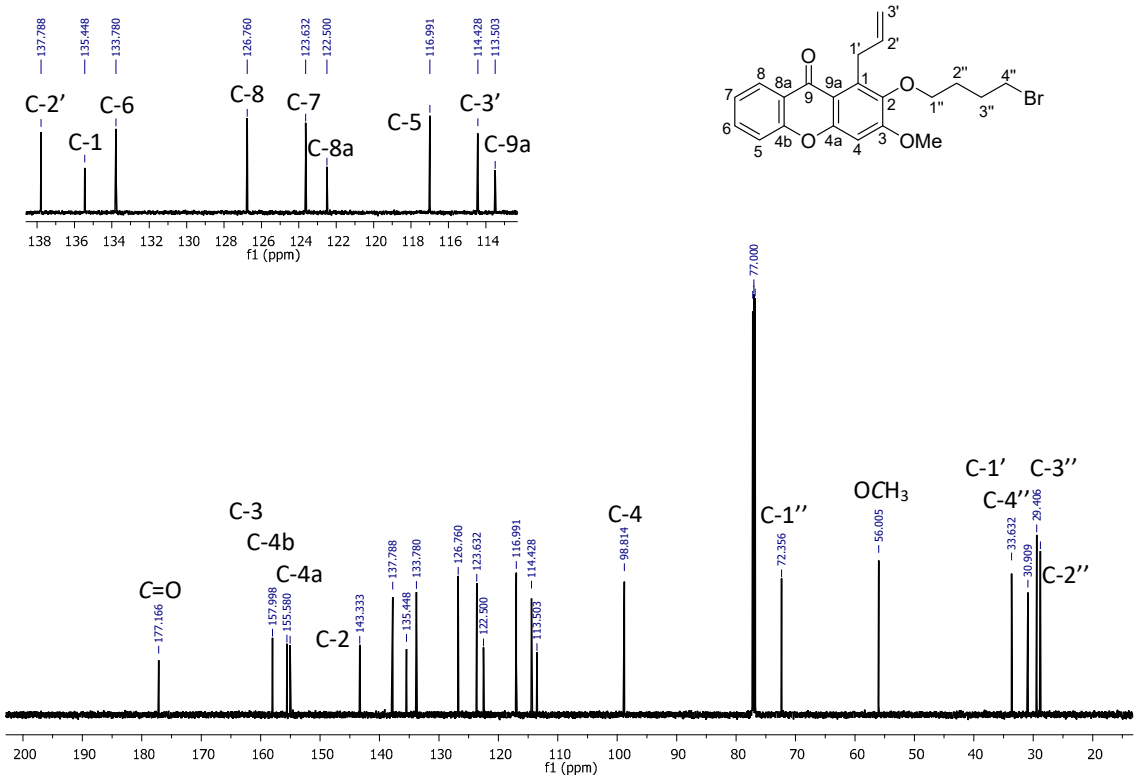
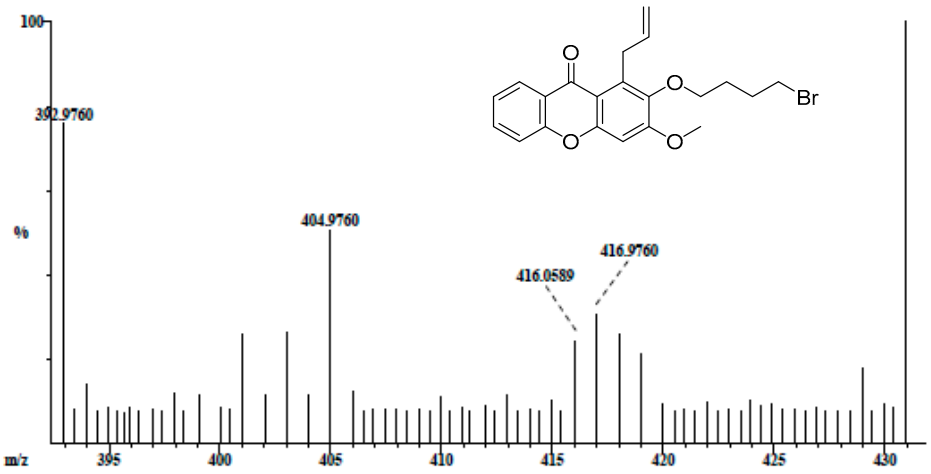


Figure S37. ^{13}C NMR (150 MHz, $CDCl_3$) spectrum of **9b**.



Selected Isotopes : $H_{0-21}C_{0-21}O_{0-4}Br_{0-1}$ Error Limit : 10 ppm Unsaturation Limits : 0 to 50

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*	*Unsaturation*
416.0589	24.2%	$C_{21}H_{21}O_4Br$	416.0623	-8.2	11.0

Figure S38. HRMS (EI) spectra of compound **9b**.

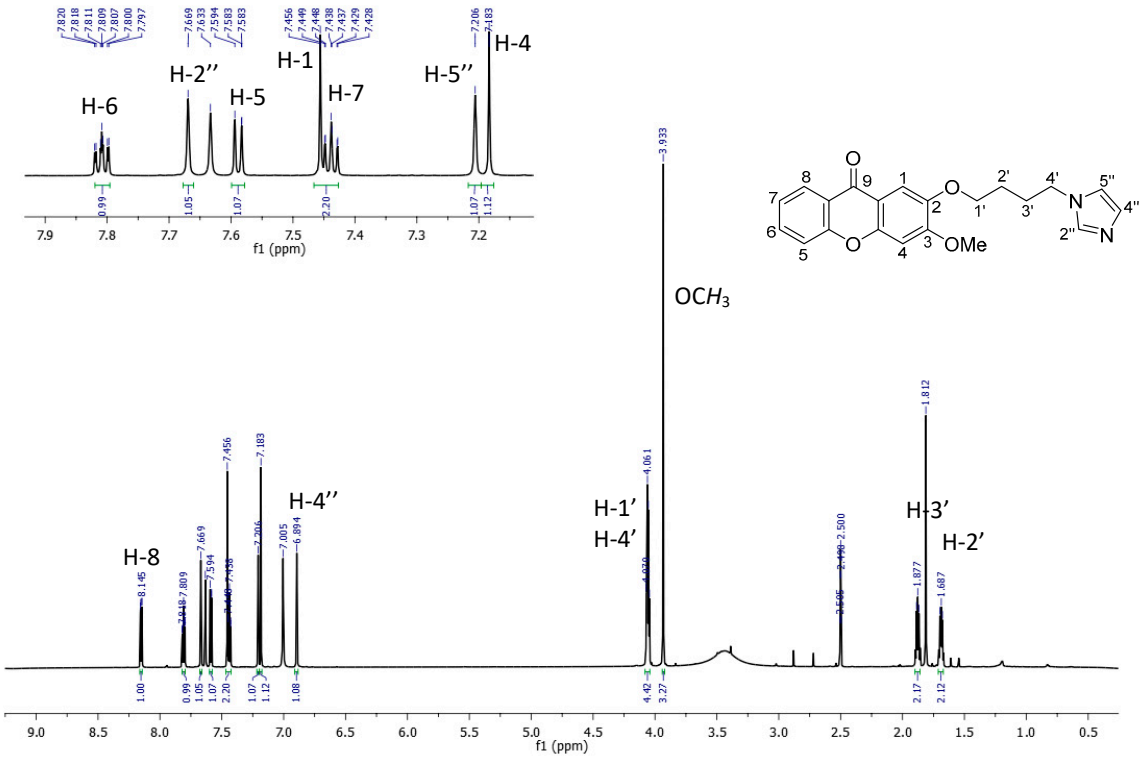


Figure S39. ^{1}H NMR (750 MHz, DMSO-d_6) spectrum of **10a**.

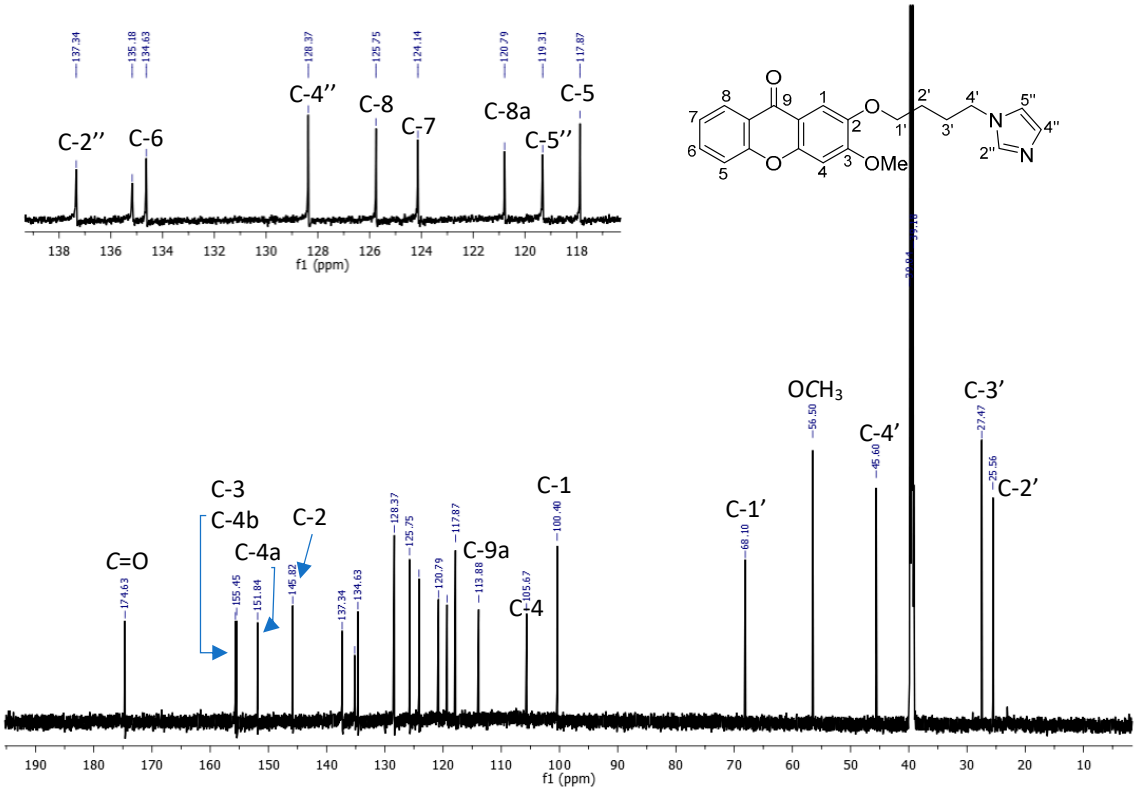
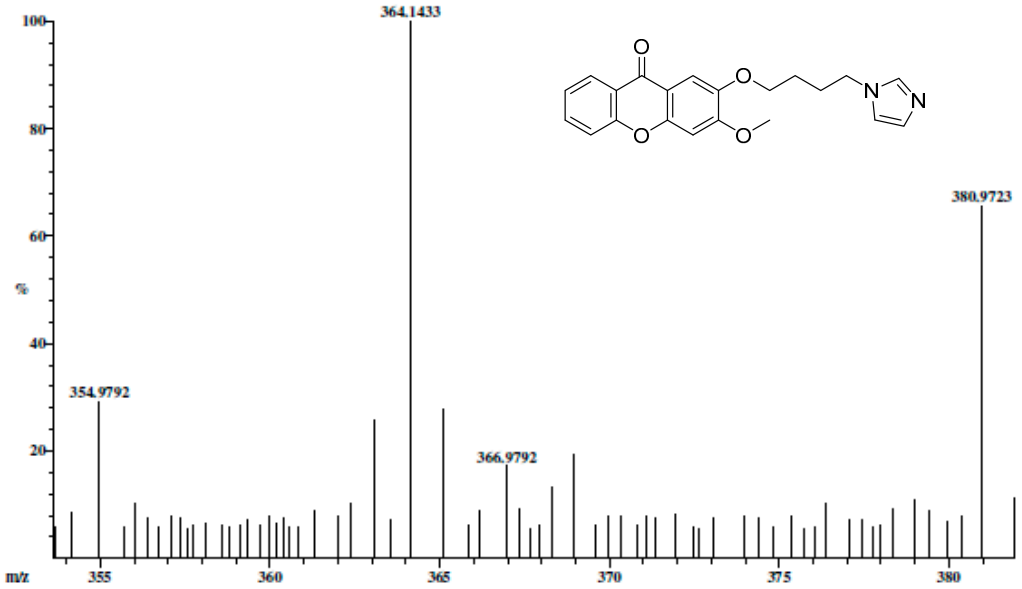


Figure S40. ^{13}C NMR (187.5 MHz, DMSO-d_6) spectrum of **10a**.



Selected Isotopes : $H_{0-20}C_{0-21}N_{0-2}O_{0-4}$ **Error Limit : 5 ppm**

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*
364.1433	100.0%	$C_{21}H_{20}N_2O_4$	364.1423	2.7

Figure S41. HRMS (EI) spectra of compound **10a**.

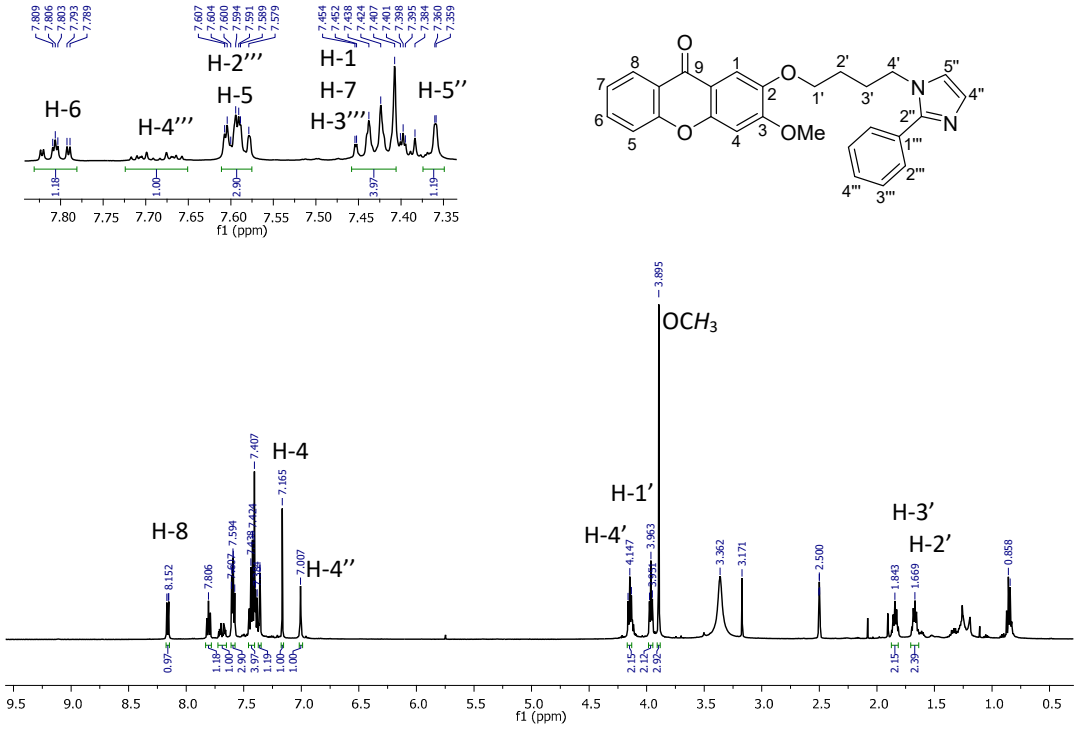


Figure S42. ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **10b**.

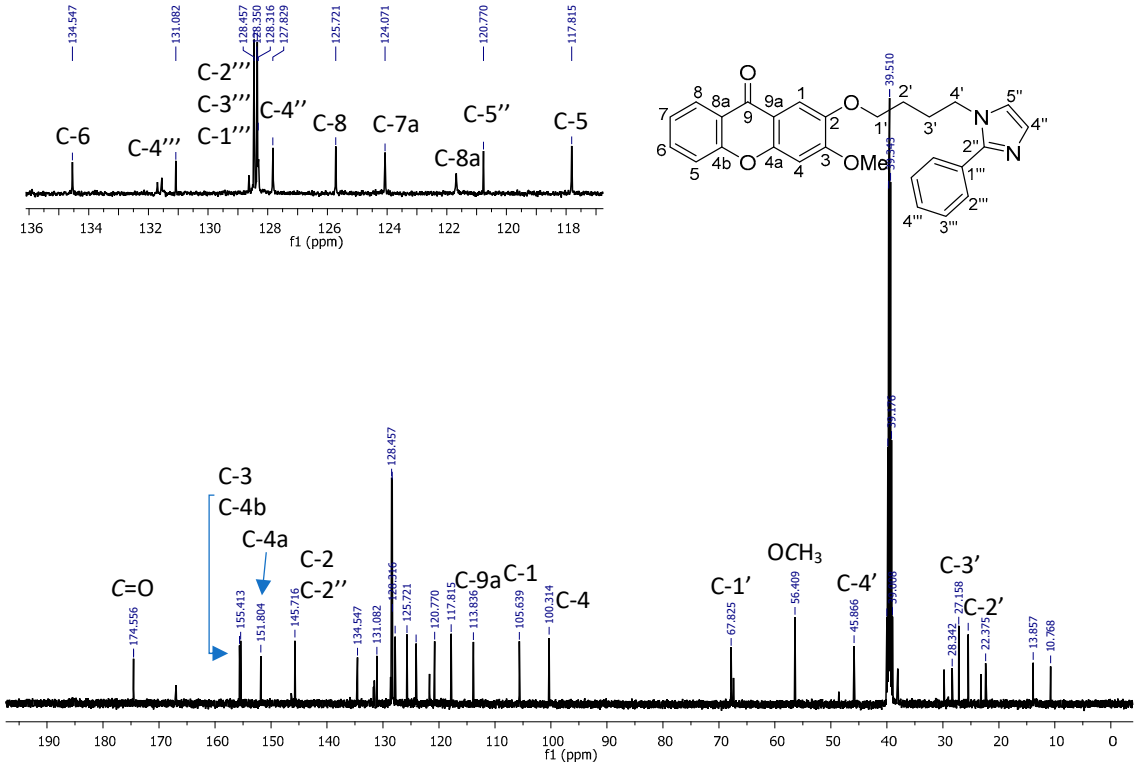
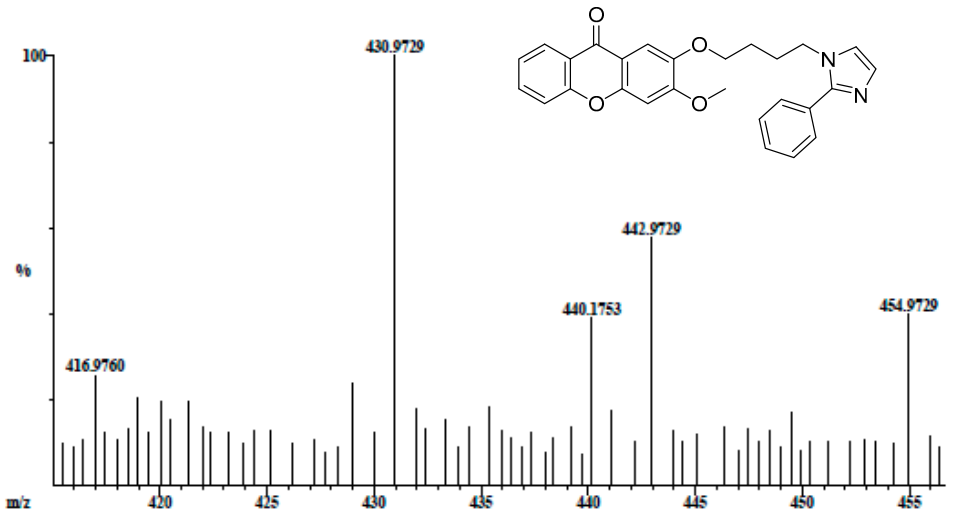


Figure S43. ^{13}C NMR (125 MHz, DMSO-d_6) spectrum of **10b**.



Selected Isotopes : $H_{0-24}C_{0-27}N_{0-2}O_{0-4}$ Error Limit : 5 ppm Unsaturation Limits : 0 to 50

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*	*Unsaturation*
440.1753	39.0%	$C_{27}H_{24}N_2O_4$	440.1736	3.8	17.0

Figure S44. HRMS (EI) spectra of compound **10b**.

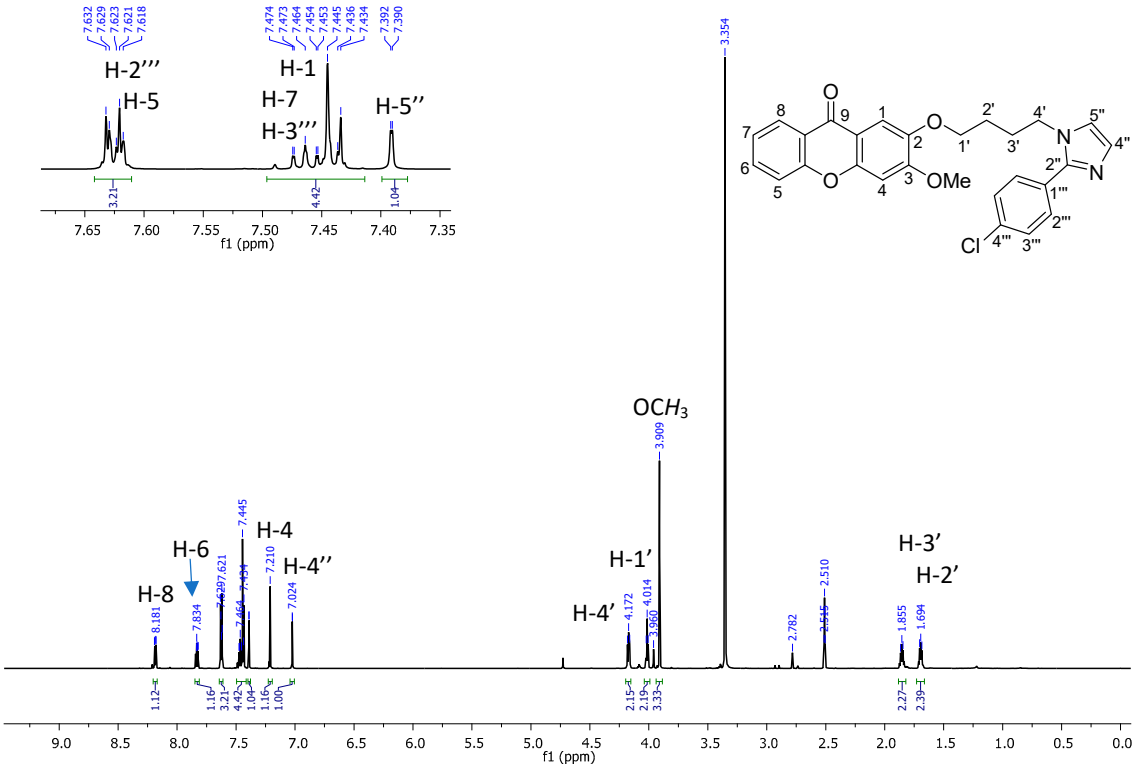


Figure S45. ^{1}H NMR (750 MHz, DMSO-d_6) spectrum of **10c**.

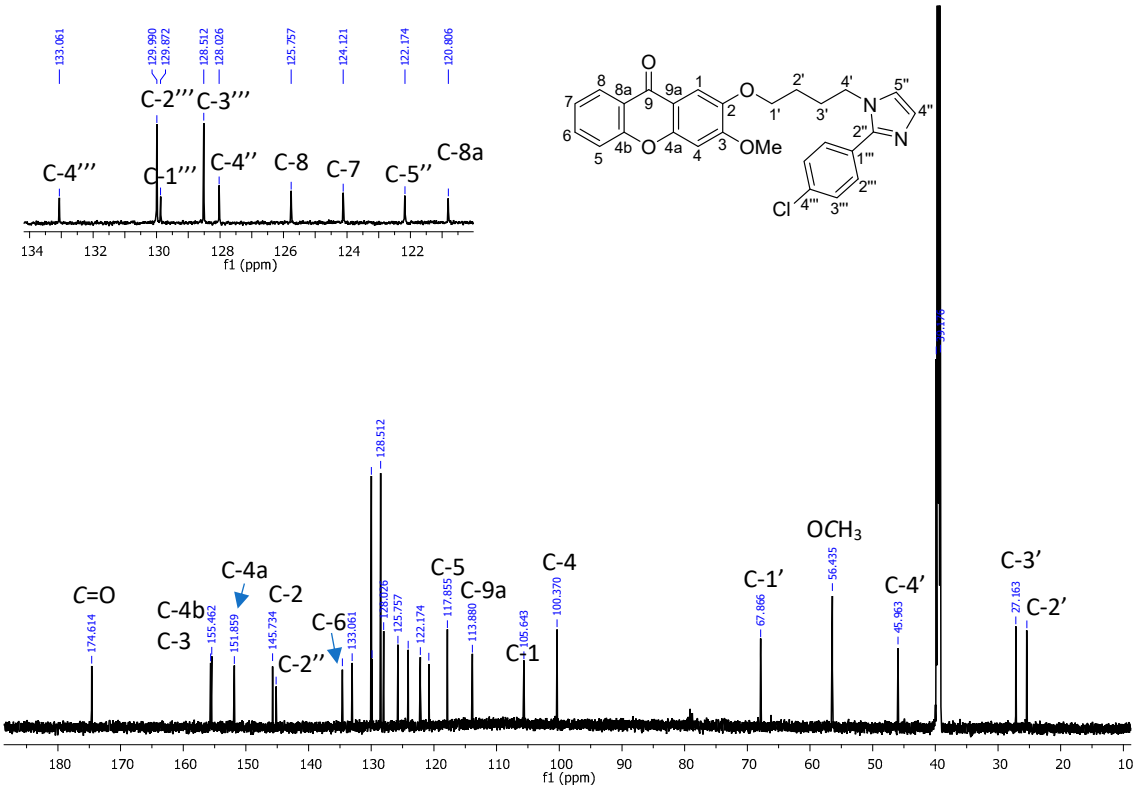
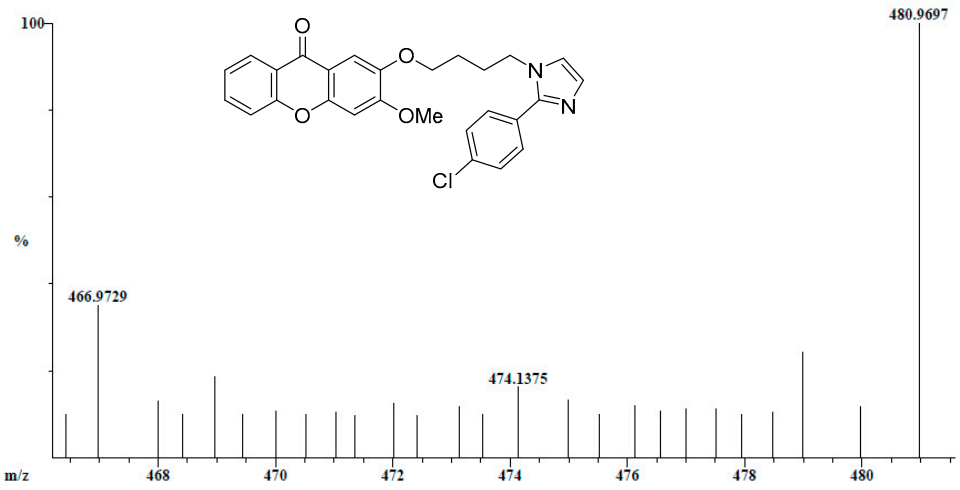


Figure S46. ^{13}C NMR (187.5 MHz, DMSO-d_6) spectrum of **10c**



Selected Isotopes : $H_{0-23}C_{0-27}N_{0-2}O_{0-4}Cl_{0-1}$ **Error Limit : 10 ppm** **Unsaturation Limits : 0 to 50**

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*	*Unsaturation*
474.1375	16.2%	$C_{27}H_{23}N_2O_4Cl$	474.1346	6.0	17.0

Figure S47. HRMS (EI) spectra of compound **10c**.

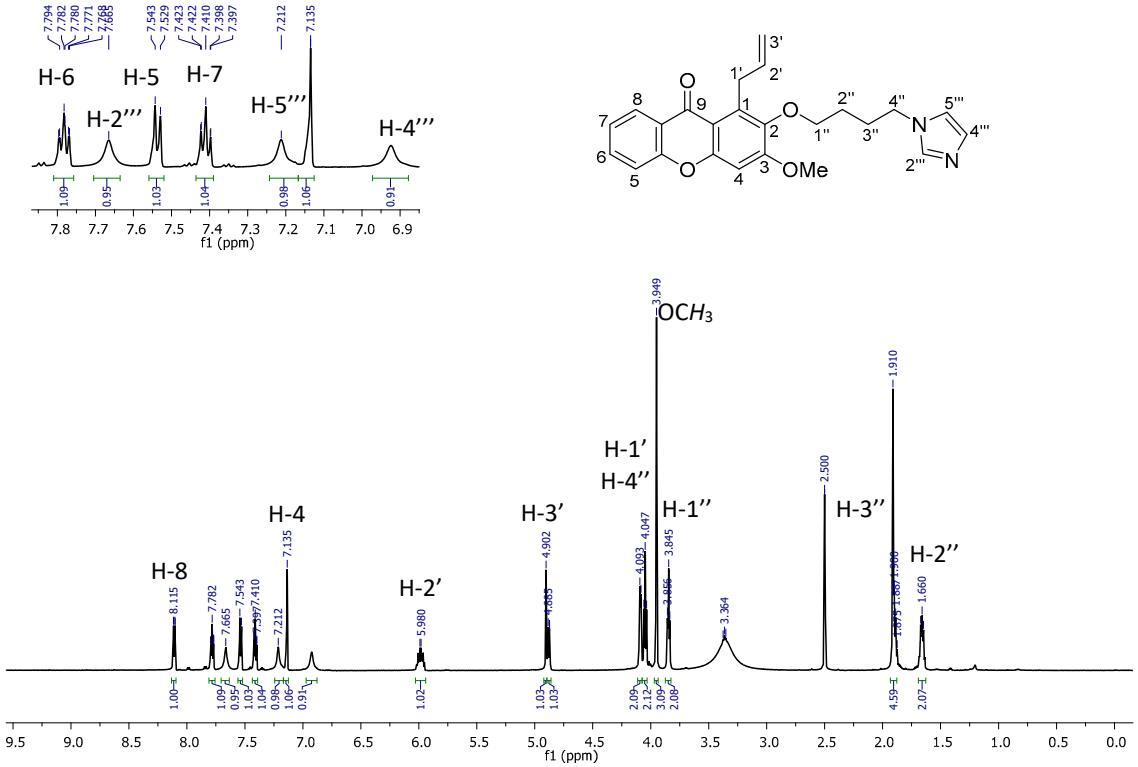


Figure S48. ^{1}H NMR (600 MHz, DMSO-d_6) spectrum of **10d**.

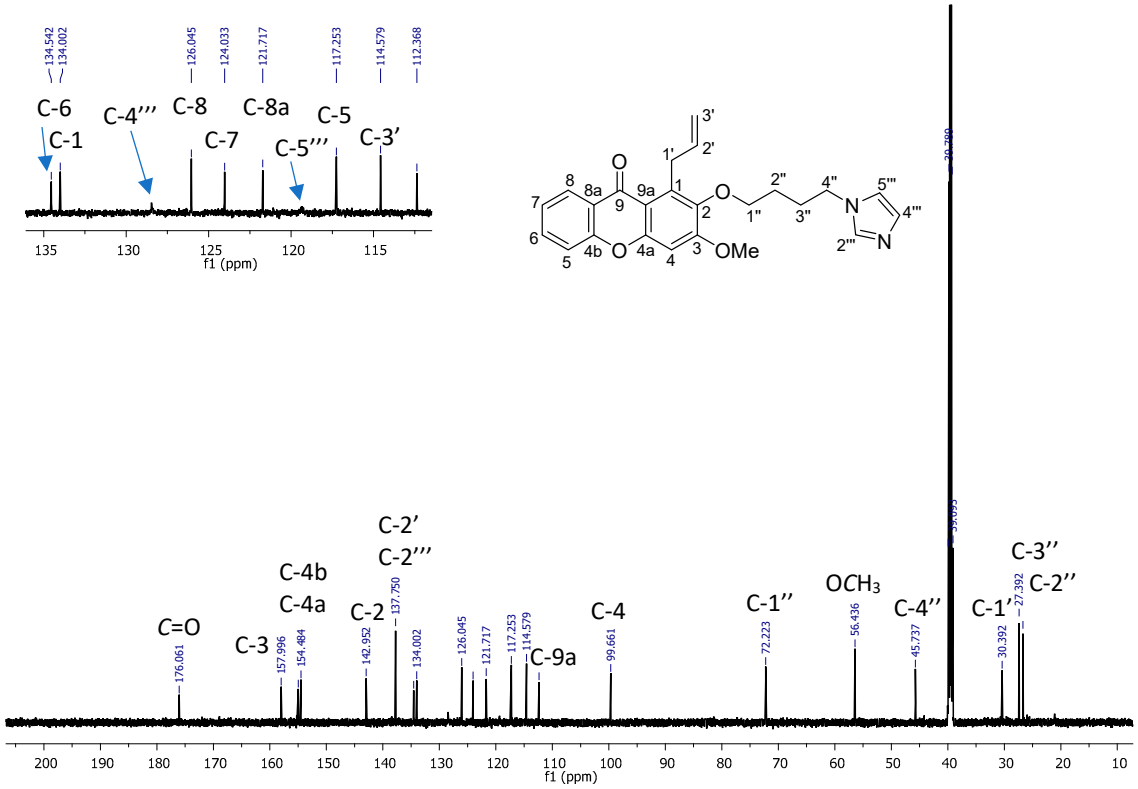
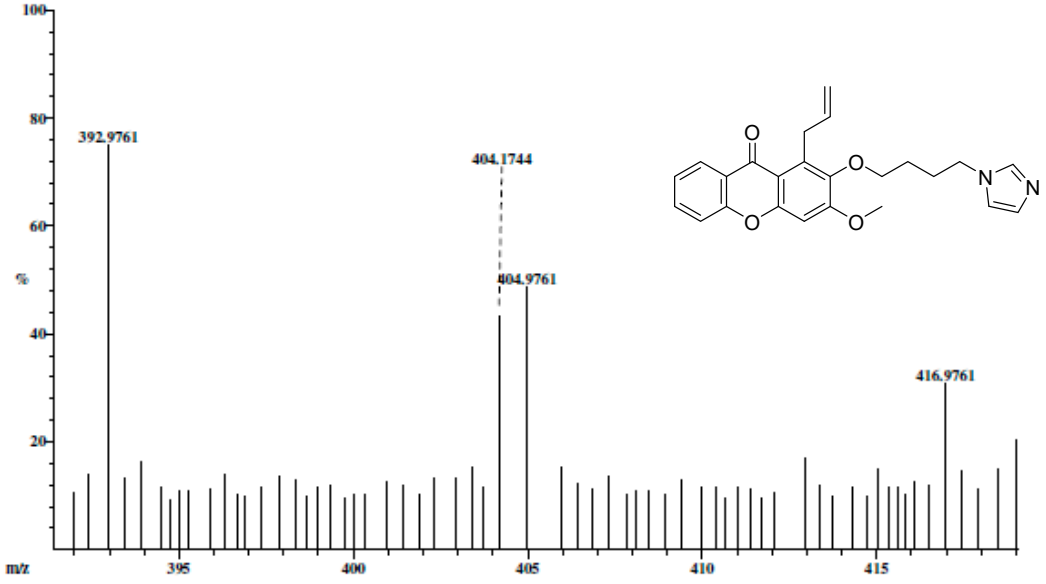


Figure S49. ^{13}C NMR (150 MHz, DMSO-d_6) spectrum of **10d**.



Selected Isotopes : $H_{0-24}C_{0-24}N_{0-2}O_{0-4}$ **Error Limit : 5 ppm**

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*
404.1744	43.2%	$C_{24}H_{24}N_2O_4$	404.1736	2.0

Figure S50. HRMS (EI) spectra of compound **10d**.

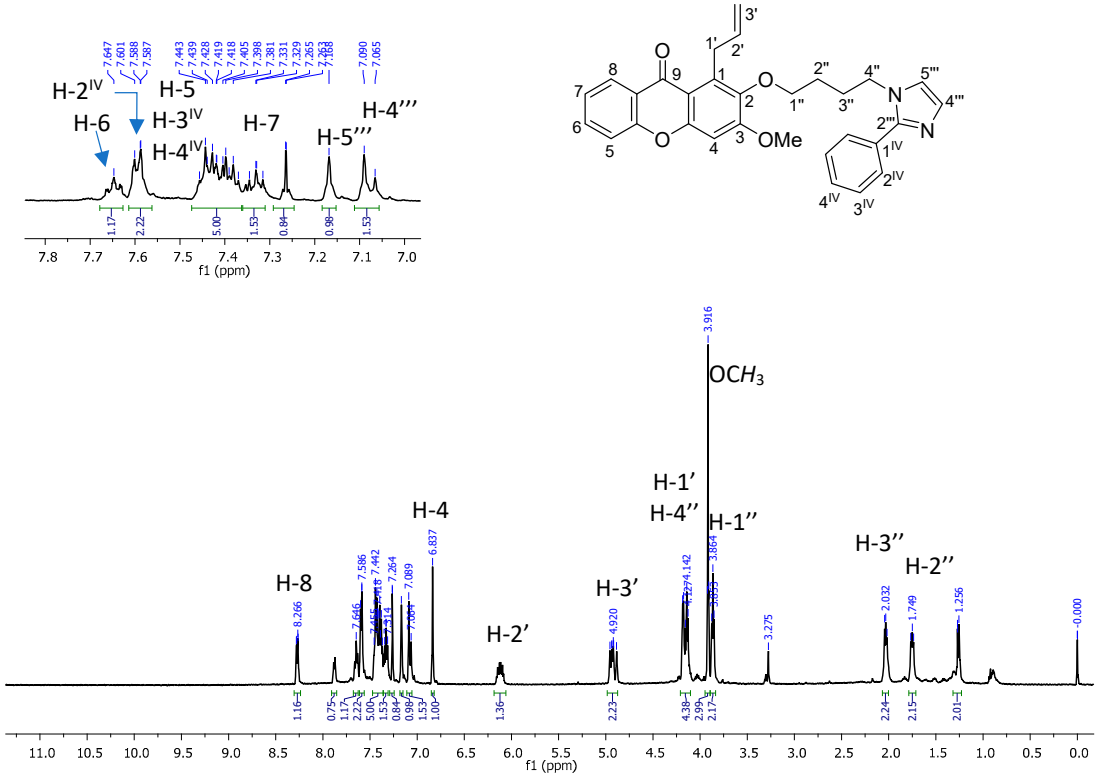


Figure S51 ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **10e**.

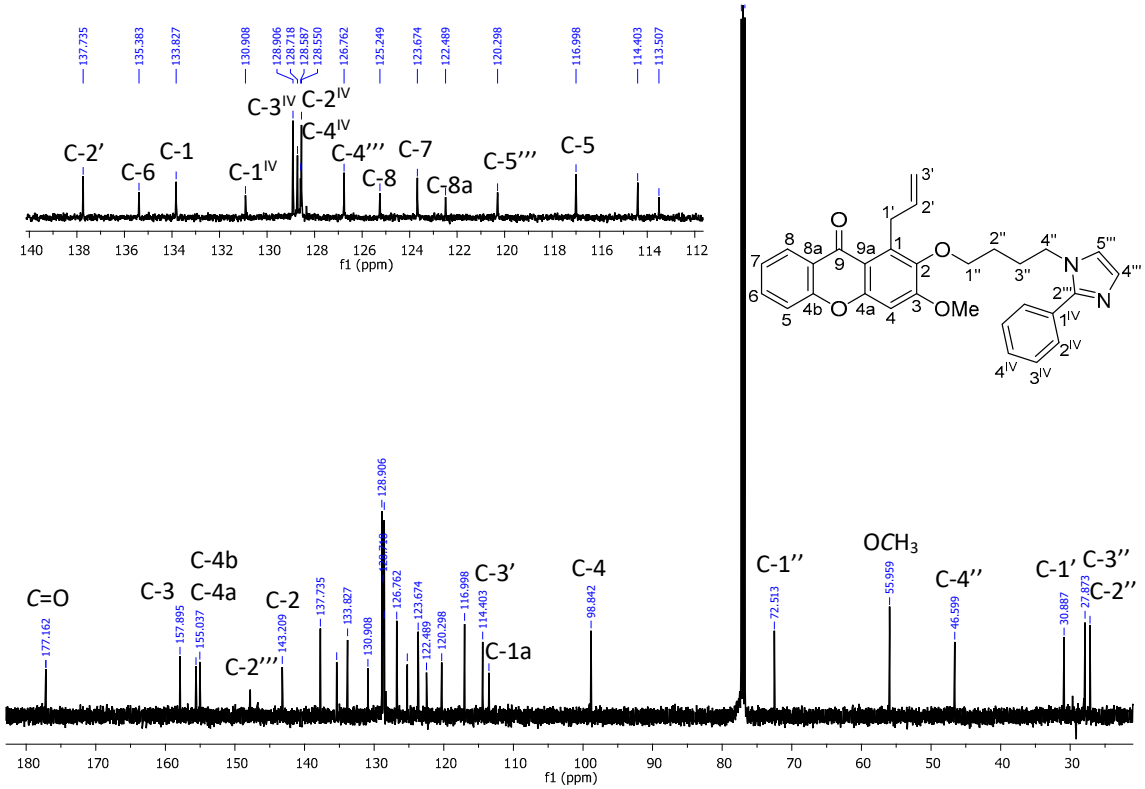
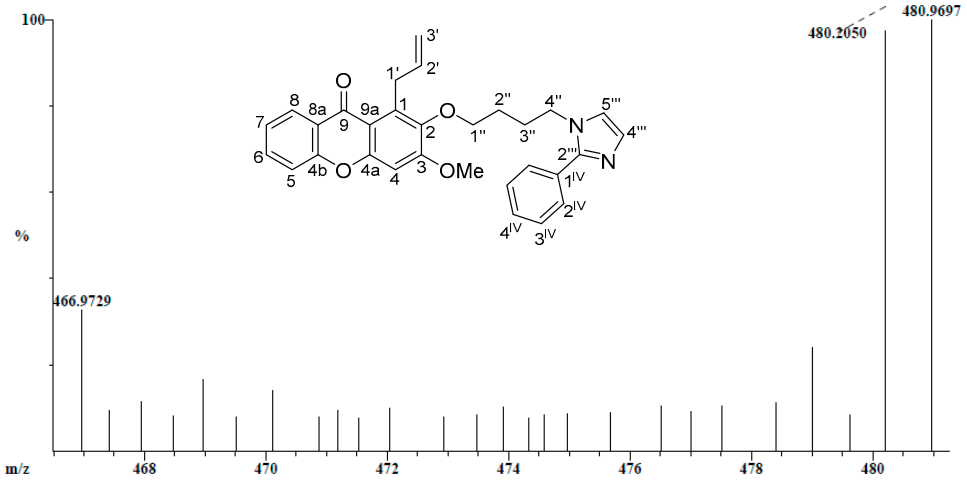


Figure S52. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **10e**.



Selected Isotopes : $H_{0-28}C_{0-30}N_{0-2}O_{0-4}$ **Error Limit : 5 ppm** **Unsaturation Limits : 0 to 50**

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*	*Unsaturation*
480.2050	97.4%	$C_{30}H_{28}N_2O_4$	480.2049	0.2	18.0

Figure S53. HRMS (EI) spectra of compound **10e**.

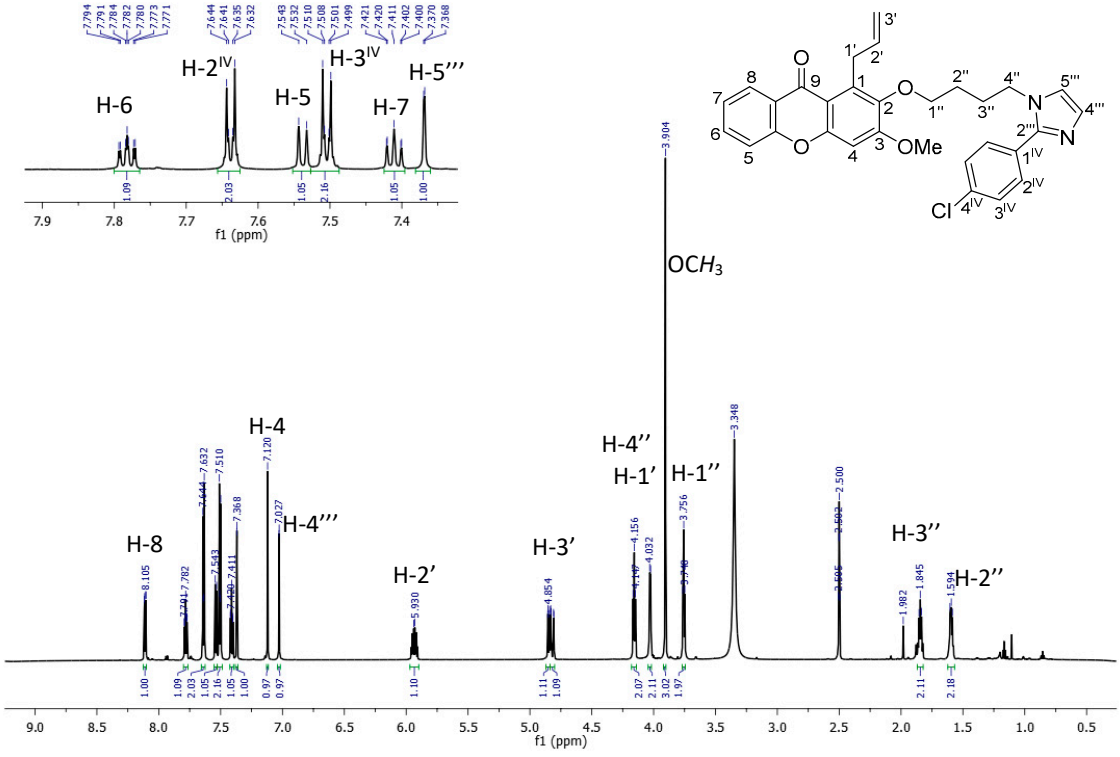


Figure S54. ^{1}H NMR (750 MHz, DMSO-d_6) spectrum of **10f**.

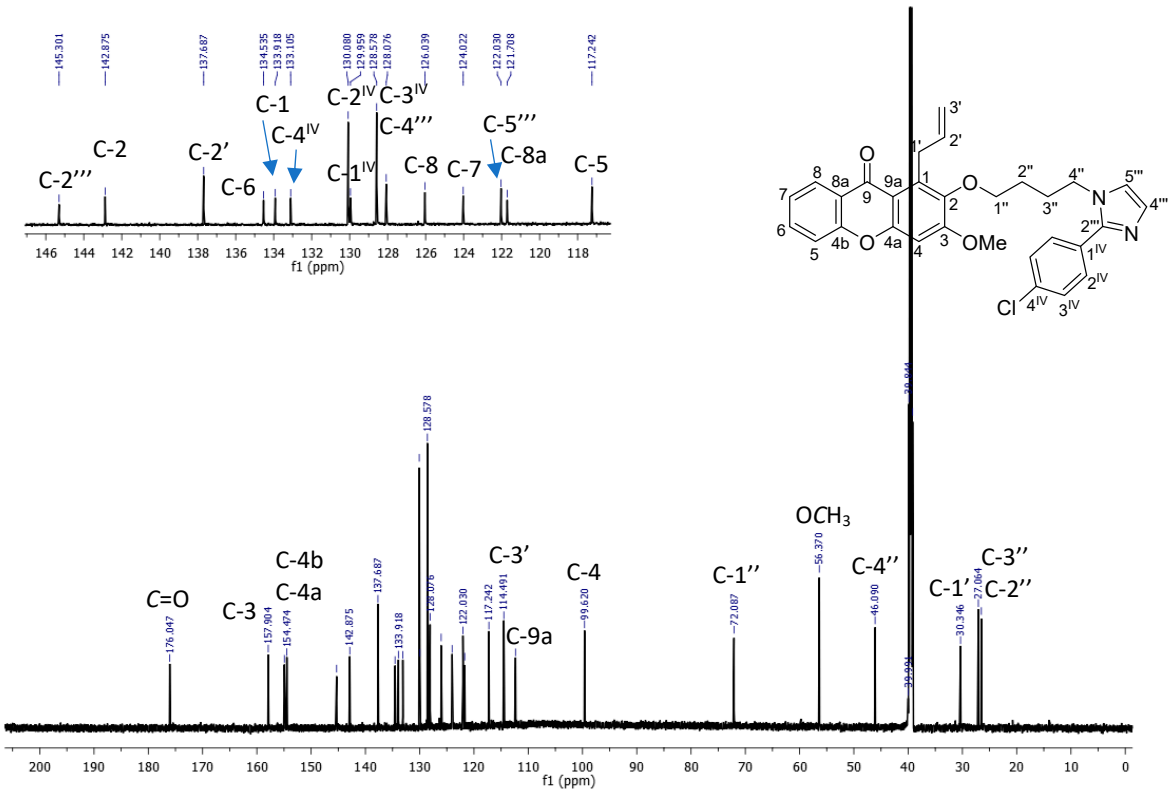
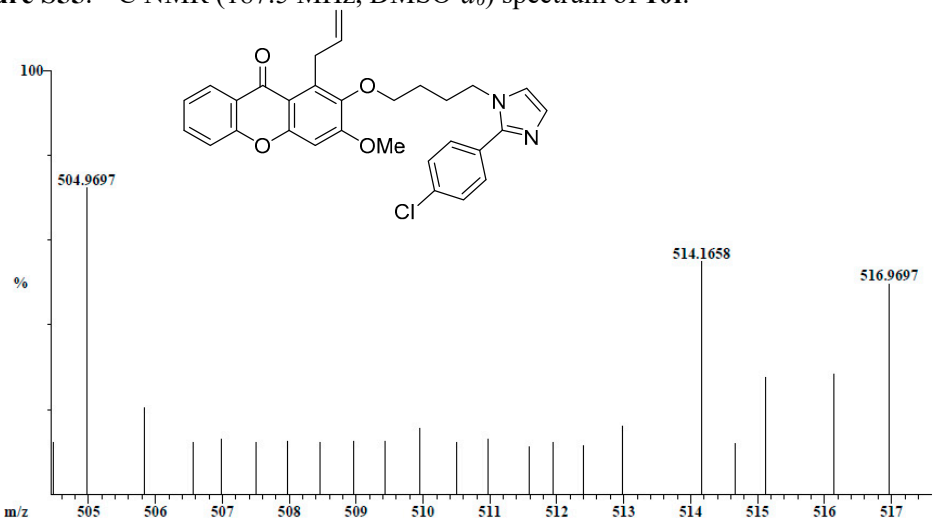


Figure S55. ^{13}C NMR (187.5 MHz, DMSO-d_6) spectrum of **10f**.



Selected Isotopes : $H_{0-27}C_{0-30}N_{0-2}O_{0-4}Cl_{0-1}$			Error Limit : 5 ppm		Unsaturation Limits : 0 to 50
Measured Mass	***% Base***	***Formula***	***Calculated Mass***	***Error***	***Unsaturation***
514.1658	**54.8%**	$C_{30}H_{27}N_2O_4Cl$	**514.1659**	**-0.3**	**18.0**

Figure S56. HRMS (EI) spectra of compound **10f**.

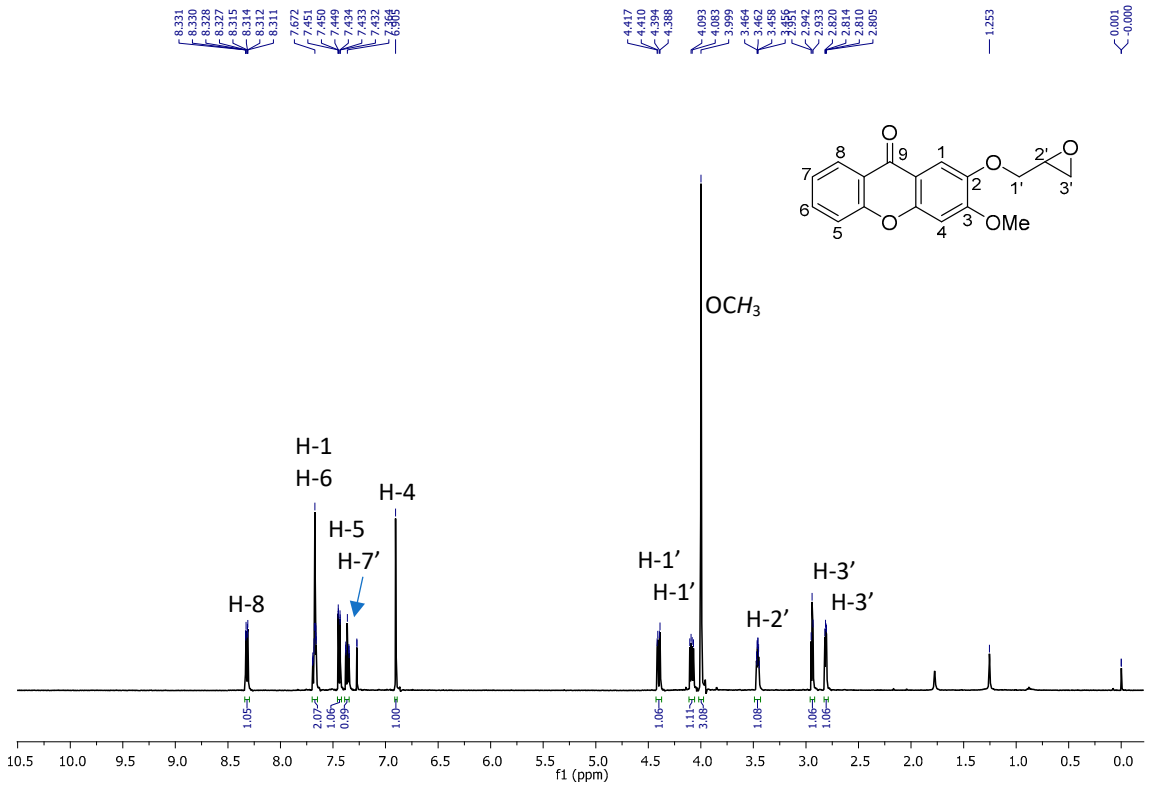


Figure S57. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **11a**.

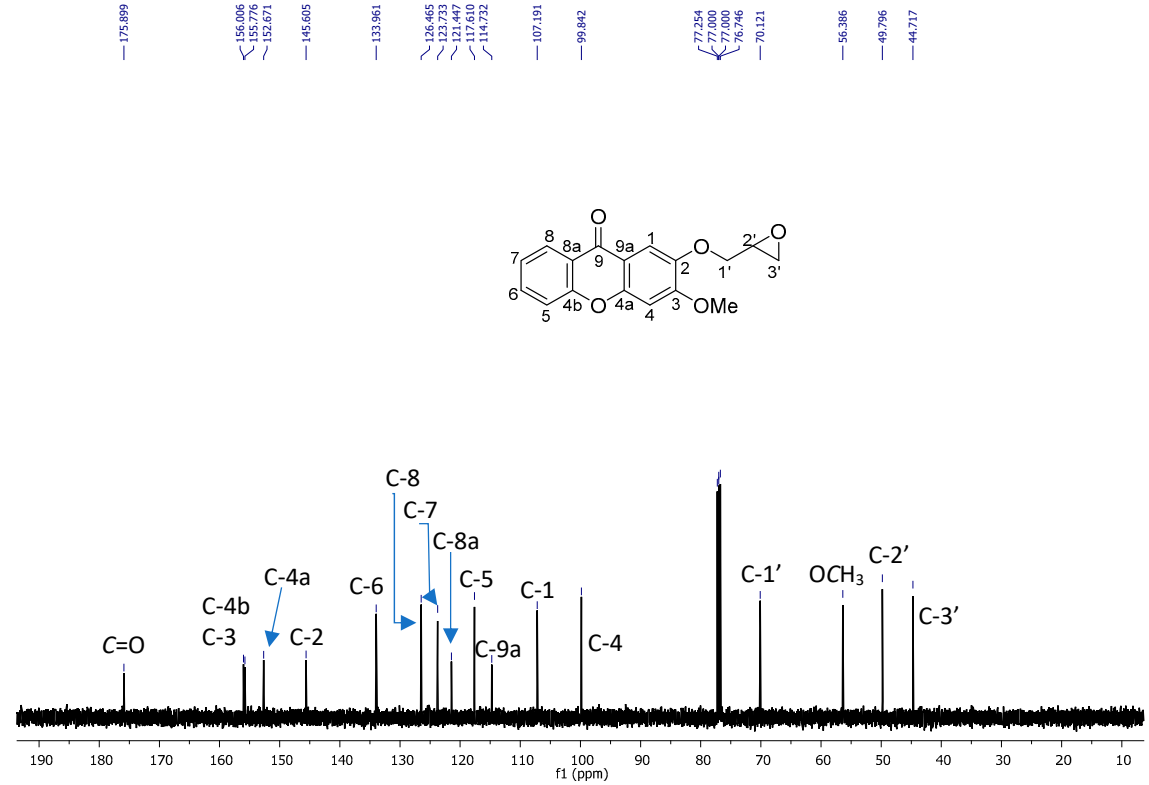
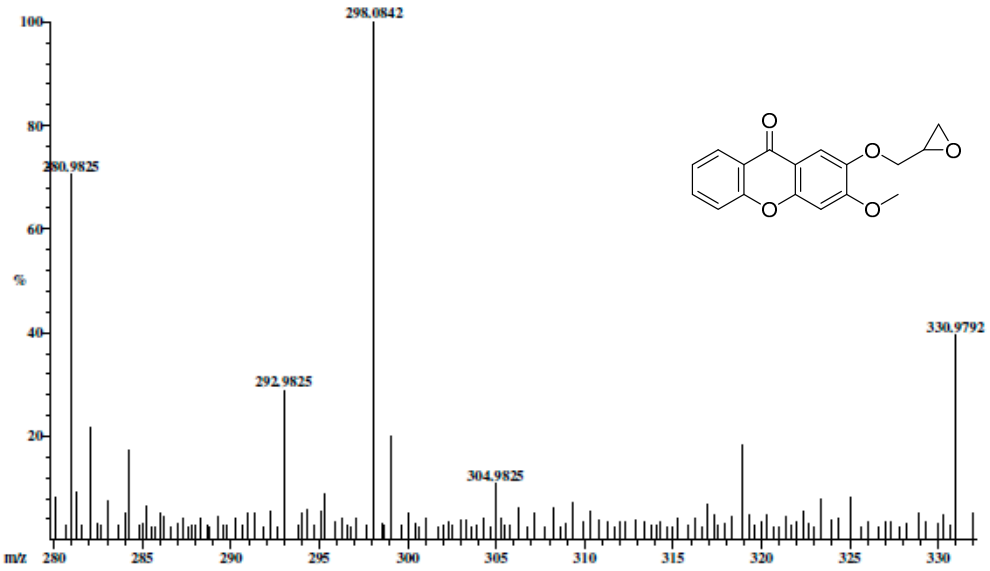


Figure S58. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **11a**.



Selected Isotopes : $H_{0-14}C_{0-17}O_{0-5}$ Error Limit : 5 ppm

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*
298.0842	100.0%	$C_{17}H_{14}O_5$	298.0841	0.3

Figure S59. HRMS (EI) spectra of compound **11a**.

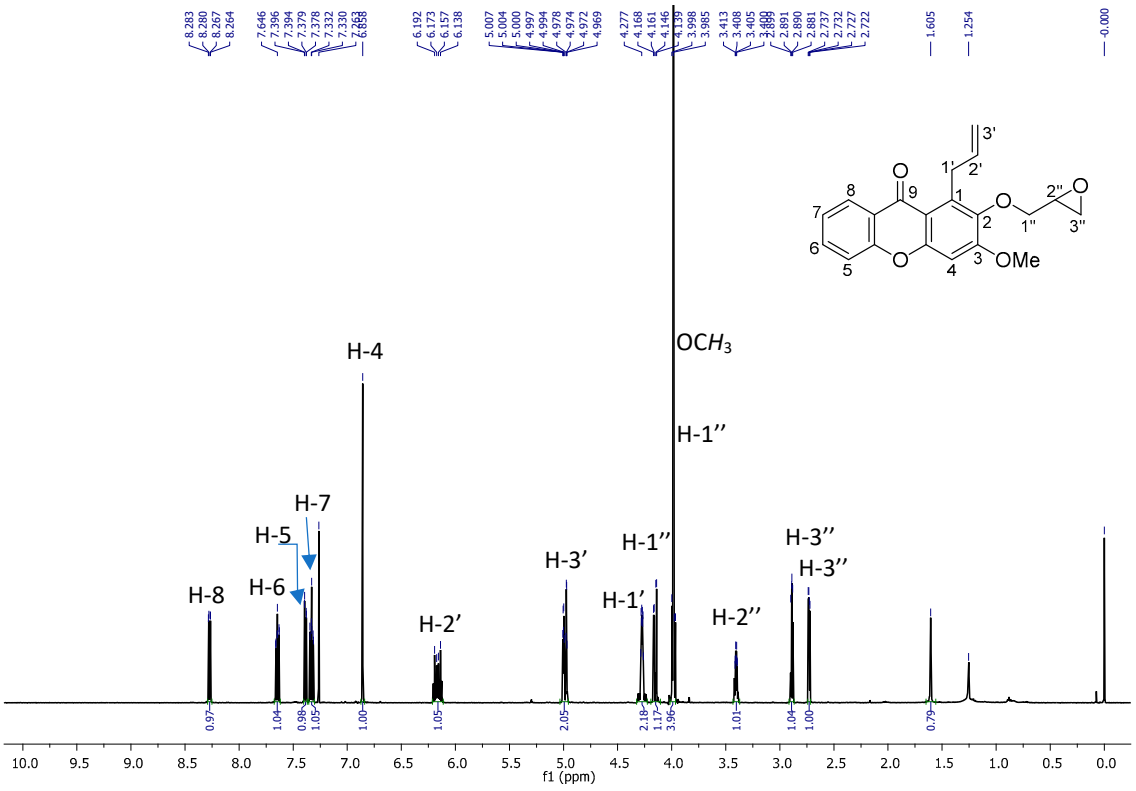


Figure S60. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **11b**.

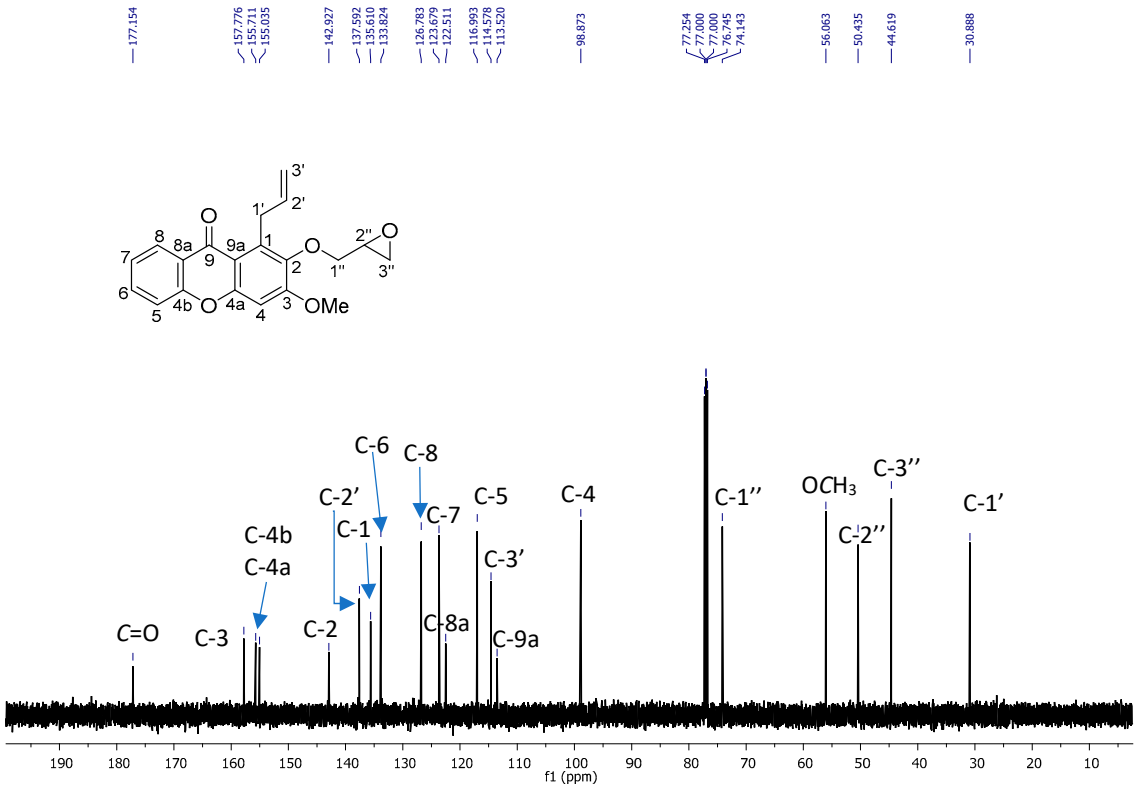
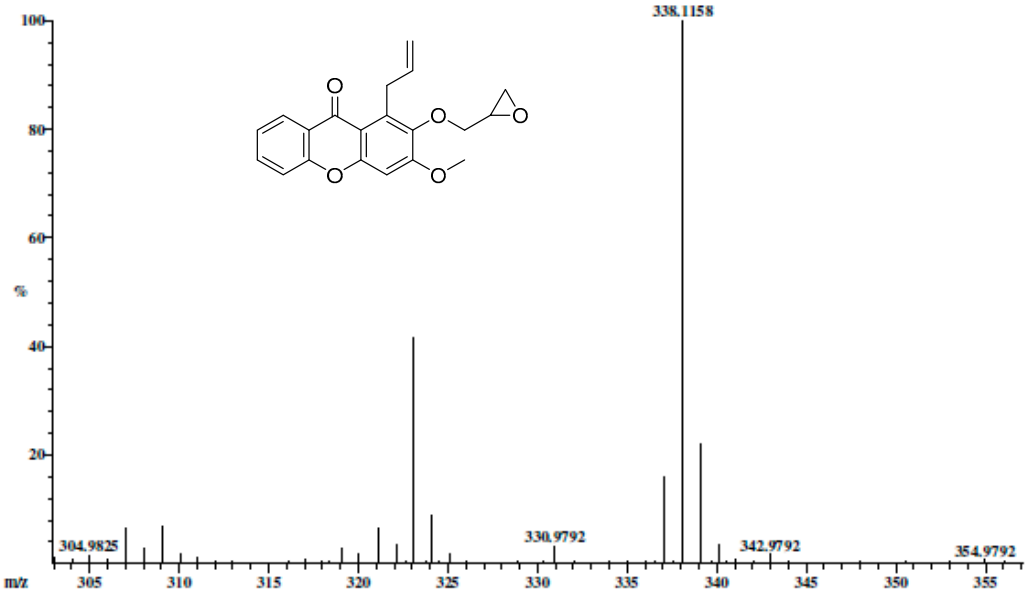


Figure S61. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **11b**.



Selected Isotopes : $H_{0-18}C_{0-20}O_{0-5}$ **Error Limit : 5 ppm**

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*
338.1158	100.0%	$C_{20}H_{18}O_5$	338.1154	1.1

Figure S62. HRMS (EI) spectra of compound **11b**.

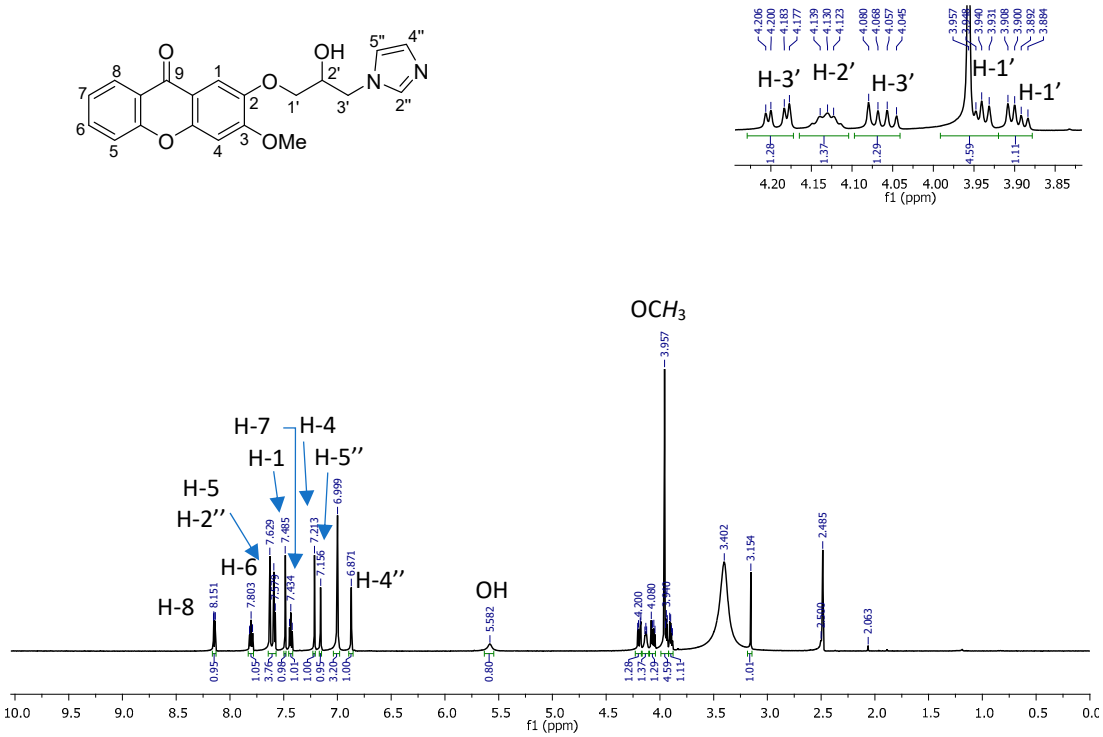


Figure S63. ^{1}H NMR (600 MHz, DMSO-d_6) spectrum of **12a**.

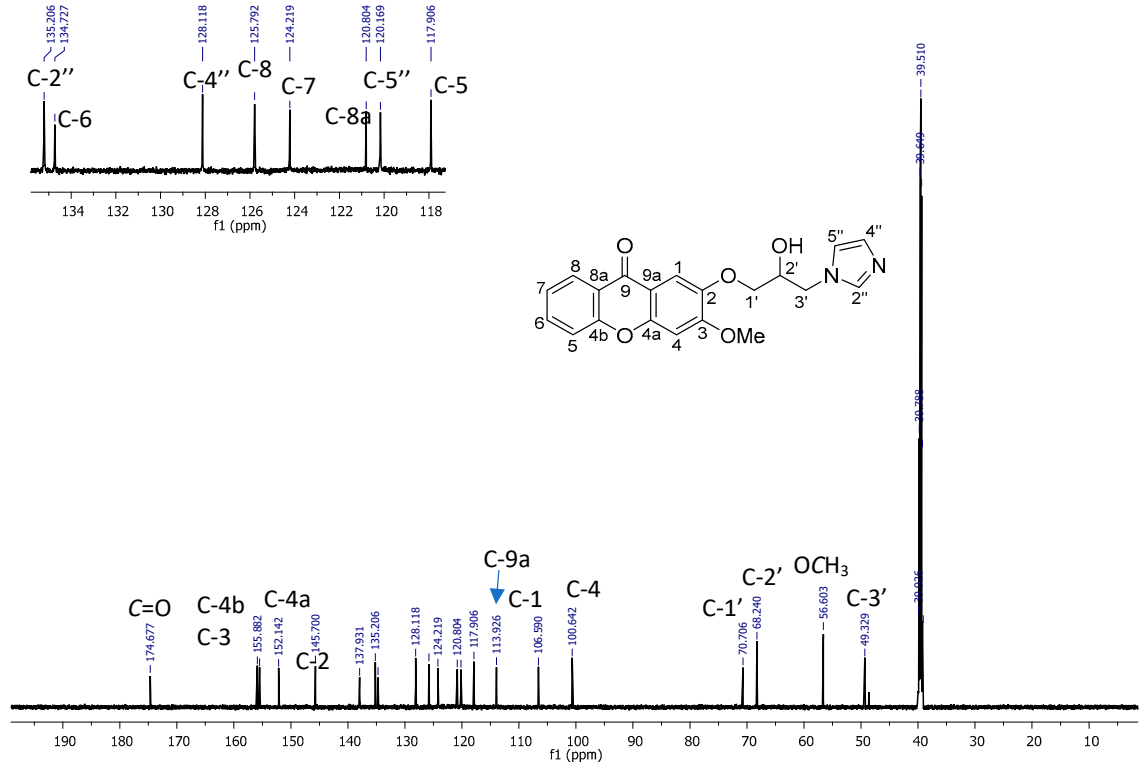
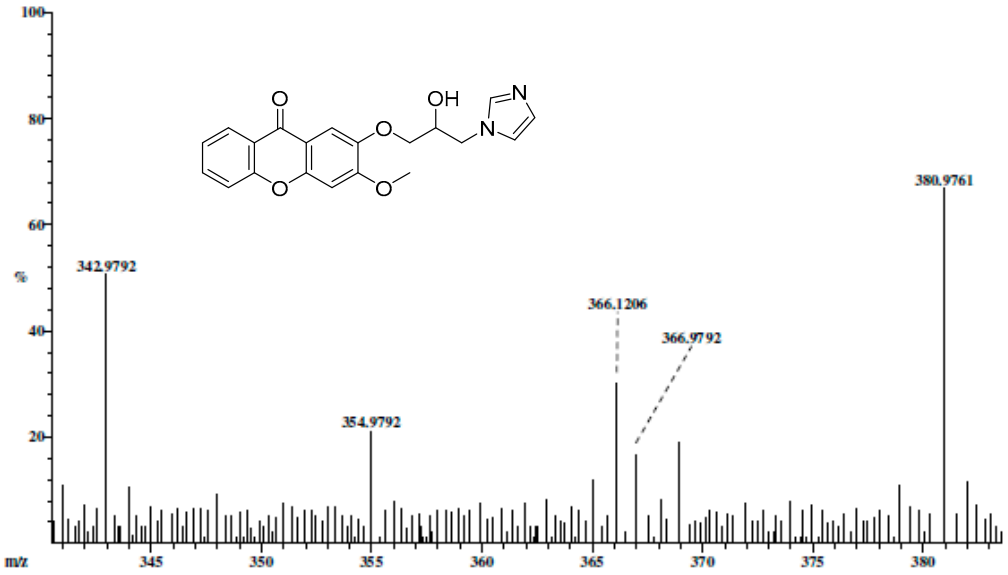


Figure S64. ^{13}C NMR (150 MHz, DMSO-d_6) spectrum of **12a.**



Selected Isotopes : $H_{0-18}C_{0-20}N_{0-2}O_{0-5}$ **Error Limit : 5 ppm**

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*
366.1206	30.1%	$C_{20}H_{18}N_2O_5$	366.1216	-2.7

Figure S65. HRMS (EI) spectra of compound **12a**.

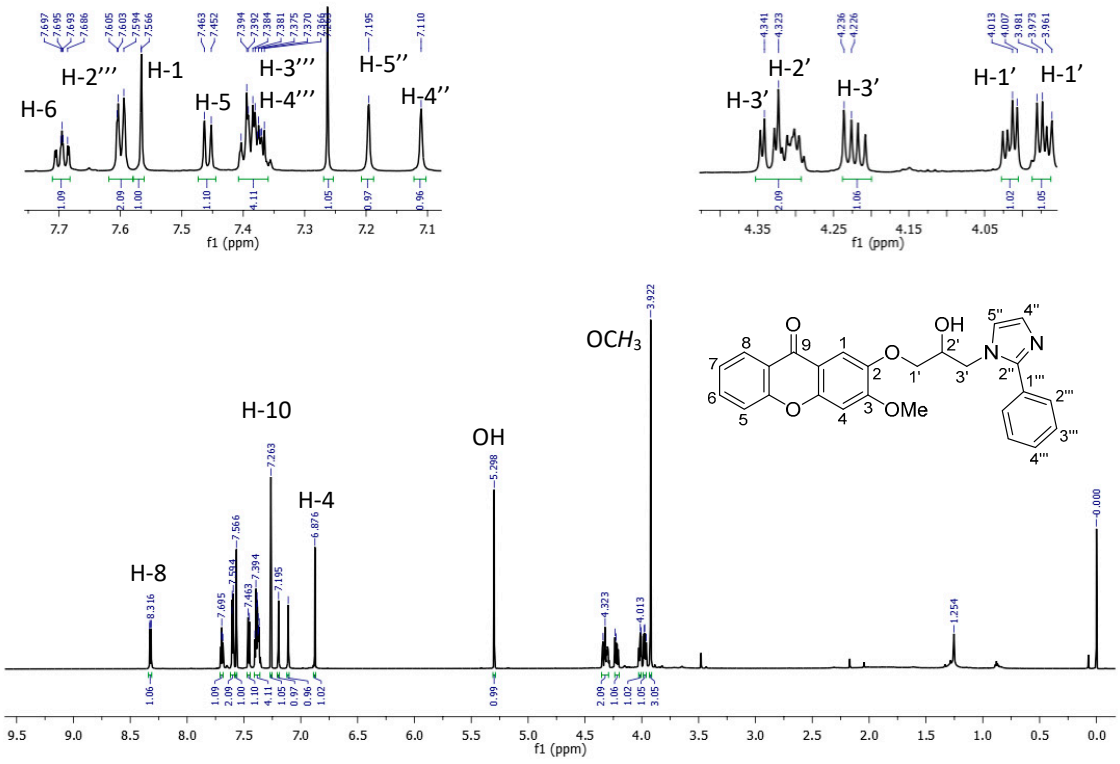


Figure S66. ^{1}H NMR (750 MHz, $CDCl_3$) spectrum of **12b**.

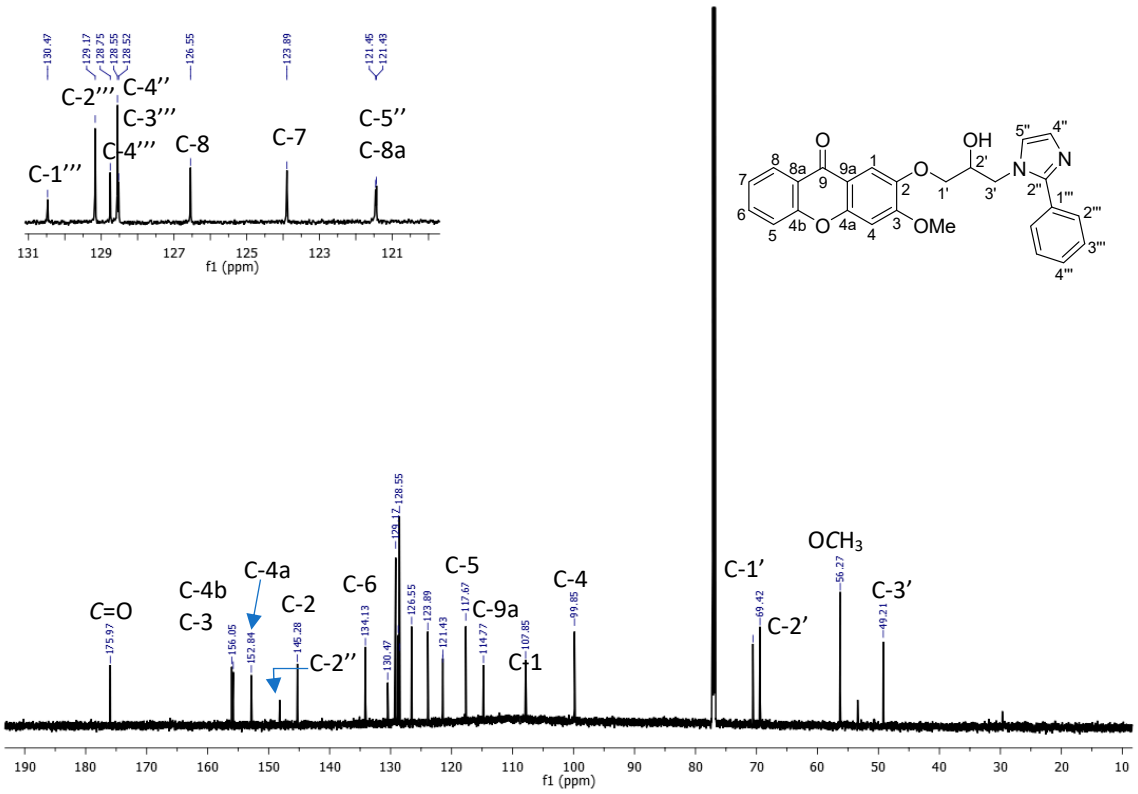
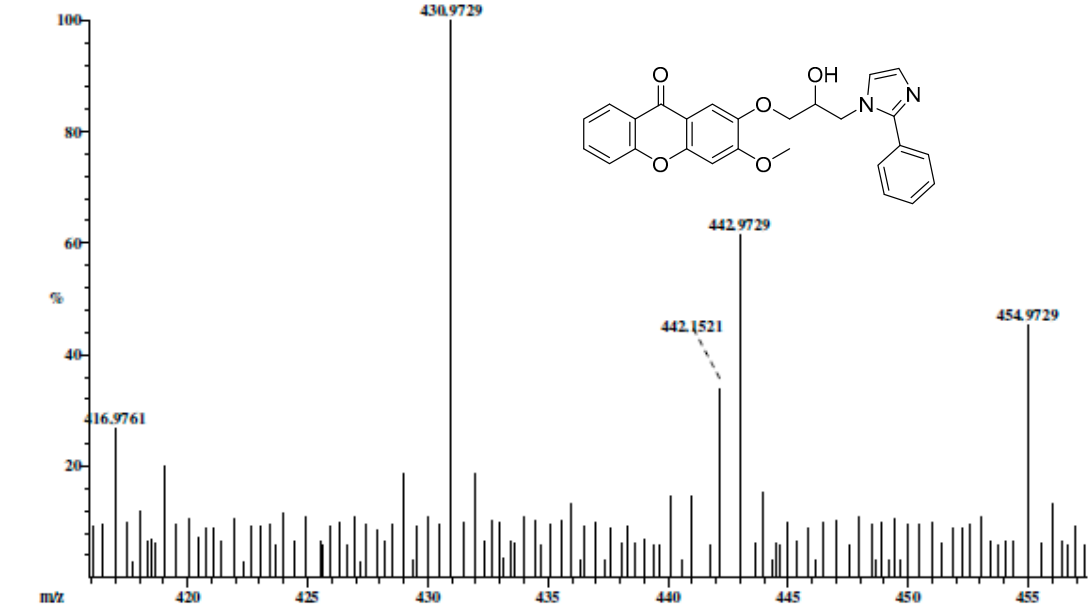


Figure S67. ^{13}C NMR (187.5 MHz, $CDCl_3$) spectrum of **12b**



Selected Isotopes : $H_{0-22}C_{0-26}N_{0-2}O_{0-5}$ **Error Limit : 5 ppm**

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*
442.1521	33.6%	$C_{26}H_{22}N_2O_5$	442.1529	-1.7

Figure S68. HRMS (EI) spectra of compound **12b**.

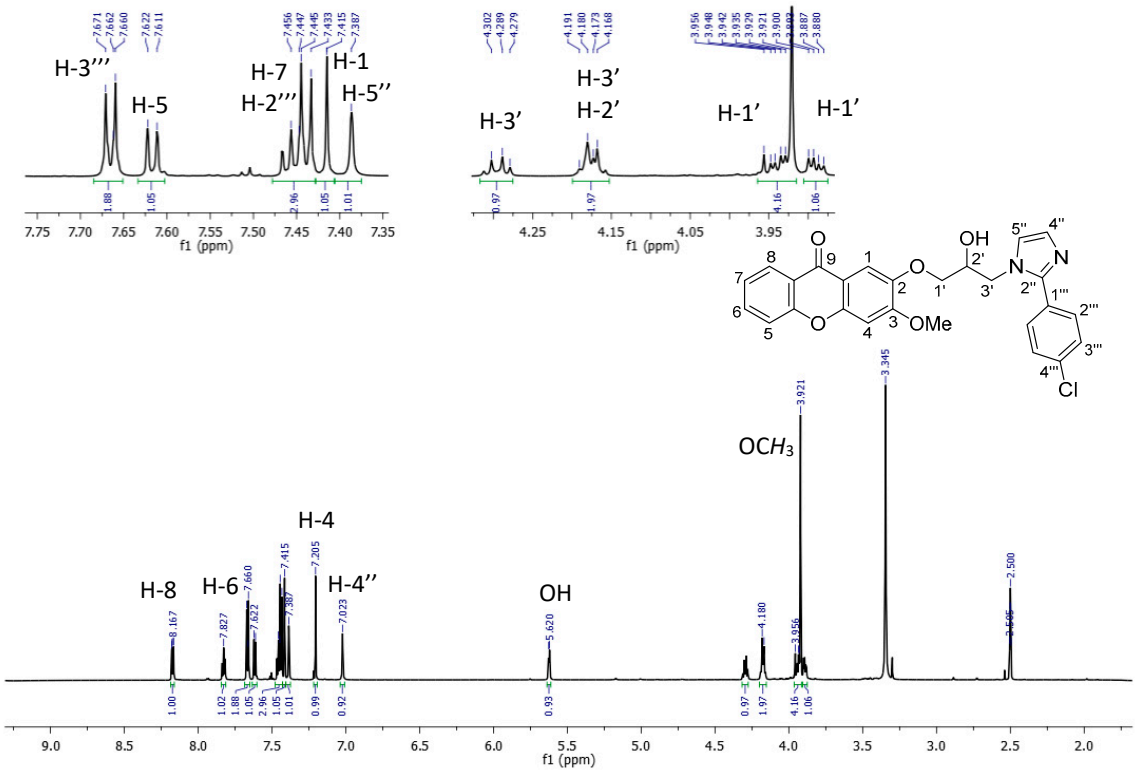


Figure S69. ^{1}H NMR (750 MHz, DMSO-d_6) spectrum of **12c**.

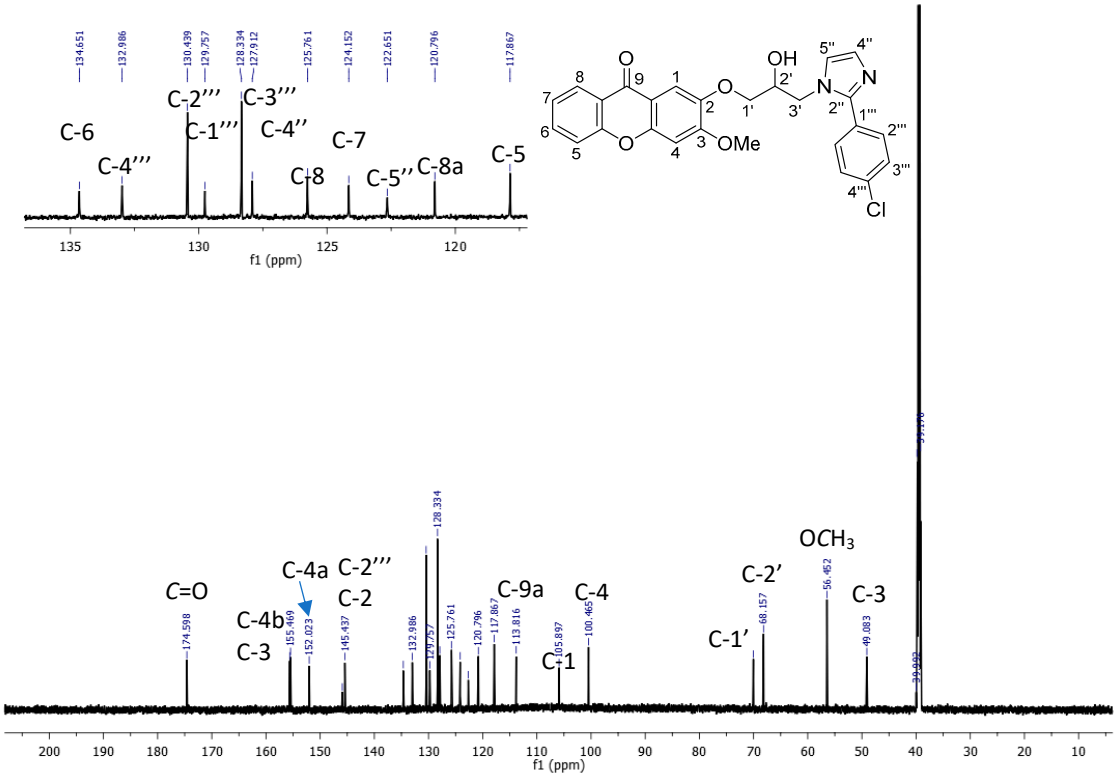
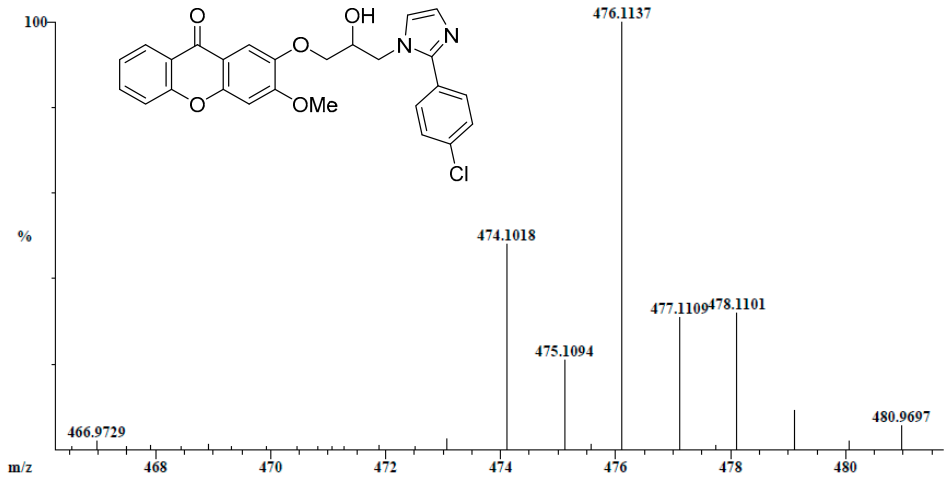


Figure S70. ^{13}C NMR (187.5 MHz, DMSO-d_6) spectrum of **12c**.



Selected Isotopes : $H_{0-21}C_{0-26}N_{0-2}O_{0-5}Cl_{0-1}$ **Error Limit : 5 ppm** **Unsaturation Limits : 0 to 50**

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*	*Unsaturation*
476.1137	100.0%	$C_{26}H_{21}N_2O_5Cl$	476.1139	-0.4	17.0

Figure S71. HRMS (EI) spectra of compound **12c**.

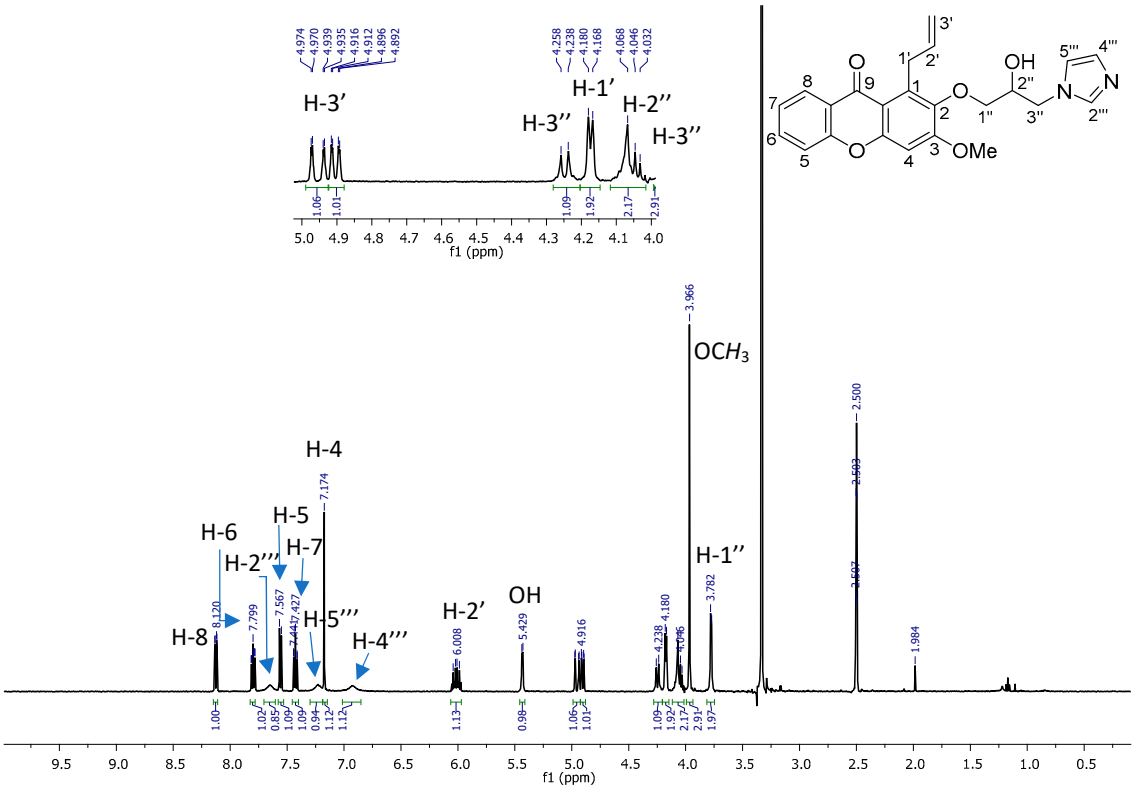


Figure S72. ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **12d**.

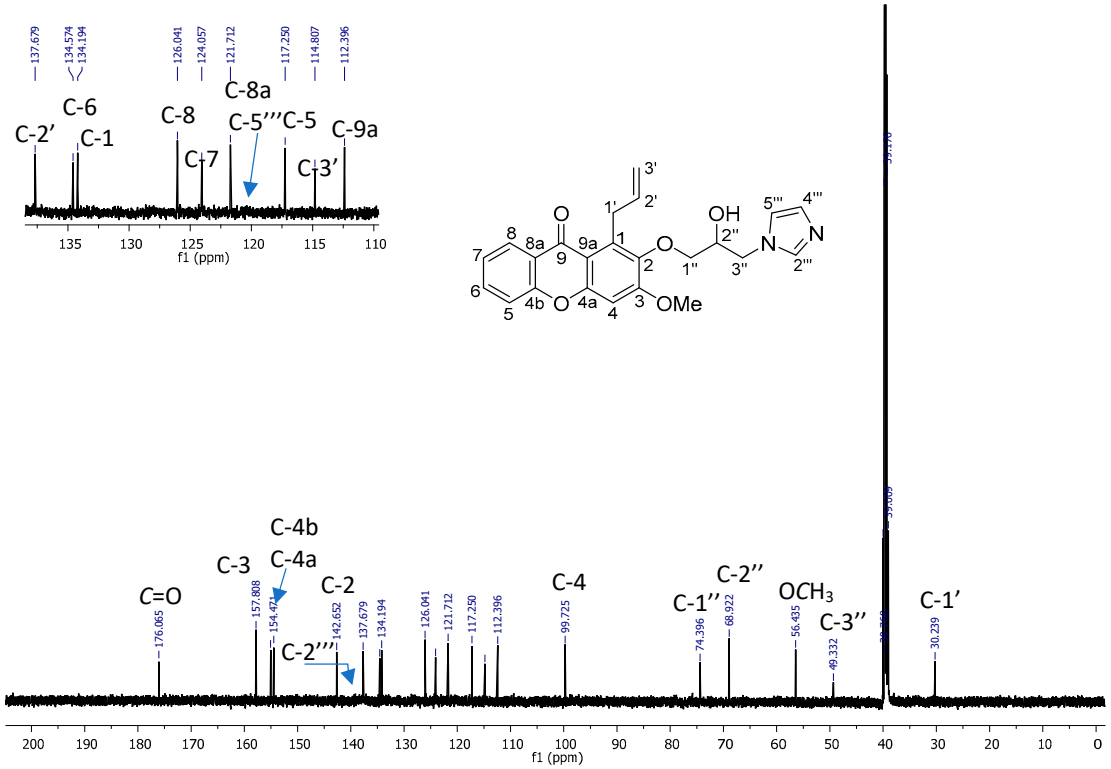
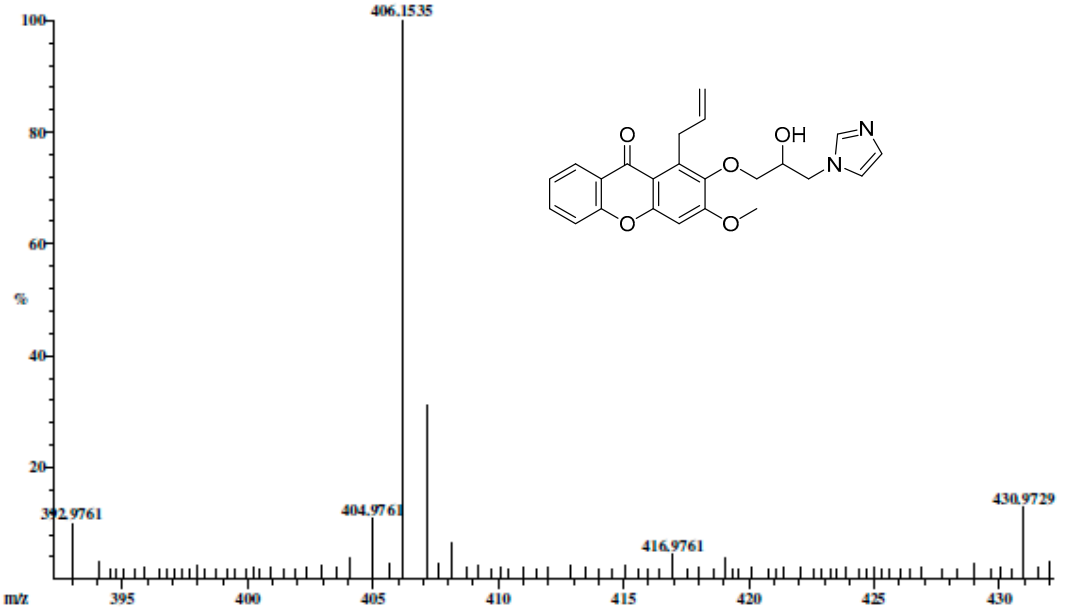


Figure S73. ^{13}C NMR (125 MHz, DMSO-d_6) spectrum of **12d**.



Selected Isotopes : $H_{0-22}C_{0-23}N_{0-2}O_{0-5}$ **Error Limit : 5 ppm**

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*
406.1535	100.0%	$C_{23}H_{22}N_2O_5$	406.1529	1.5

Figure S74. HRMS (EI) spectra of compound **12d**.

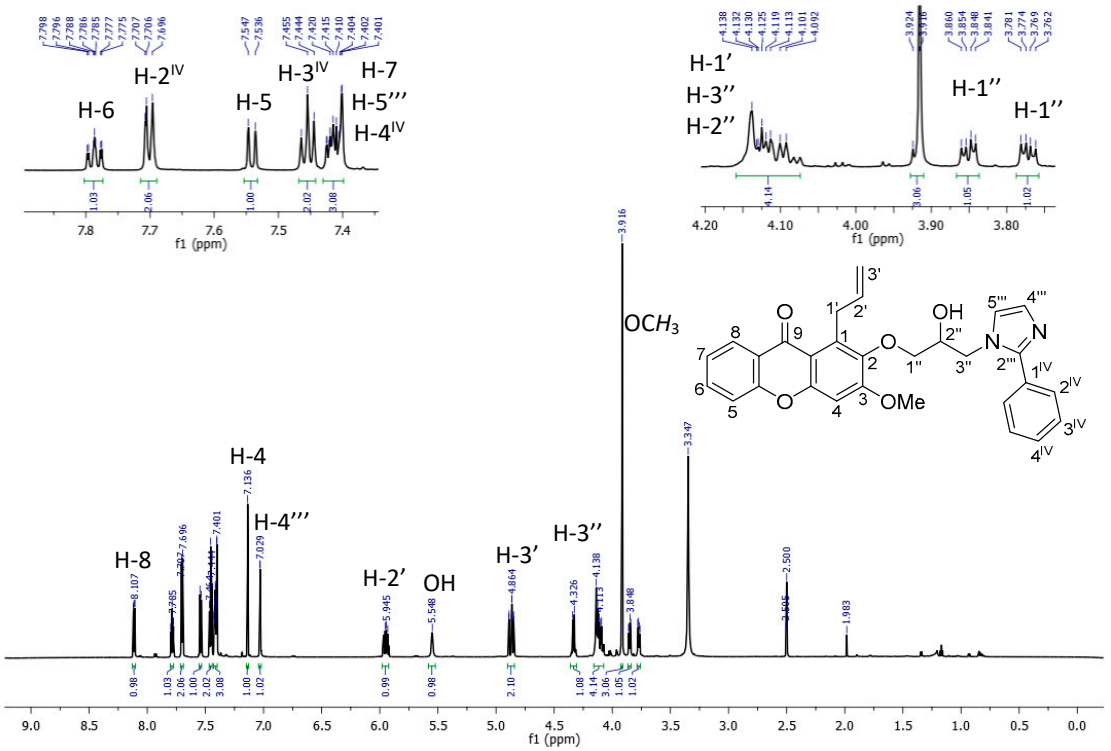


Figure S75. ^{1}H NMR (750 MHz, DMSO-d_6) spectrum of **12e**.

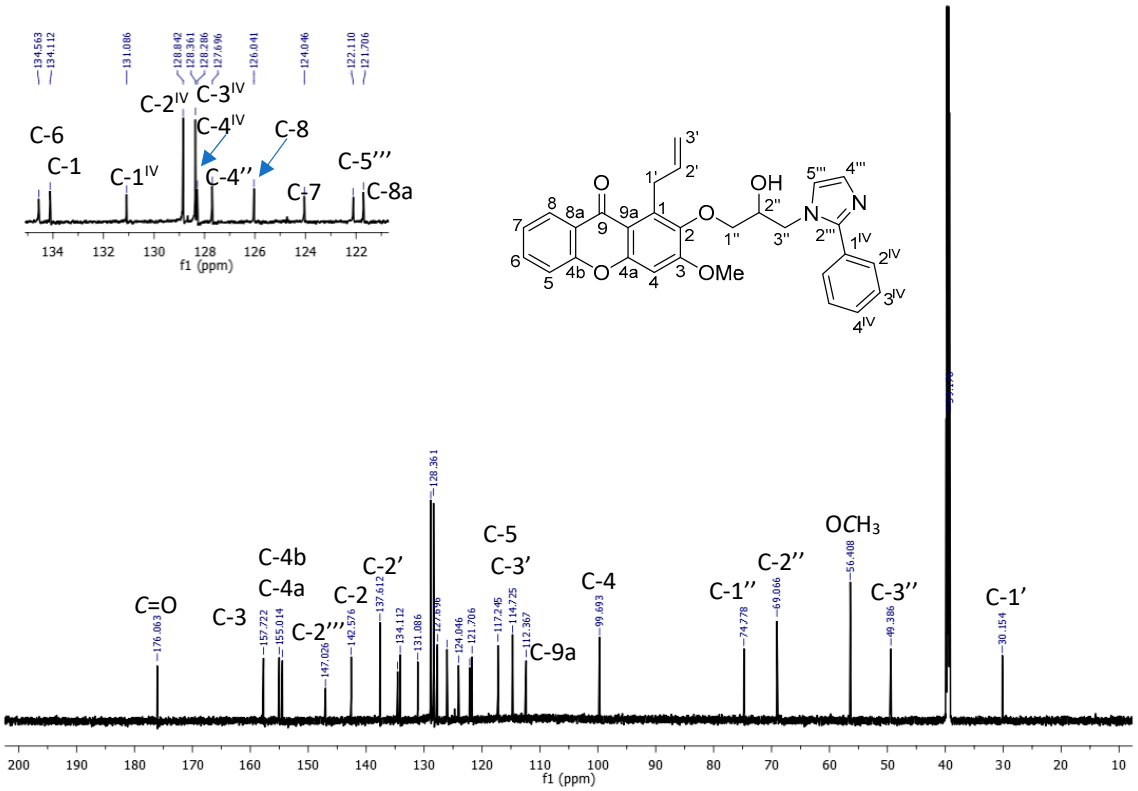
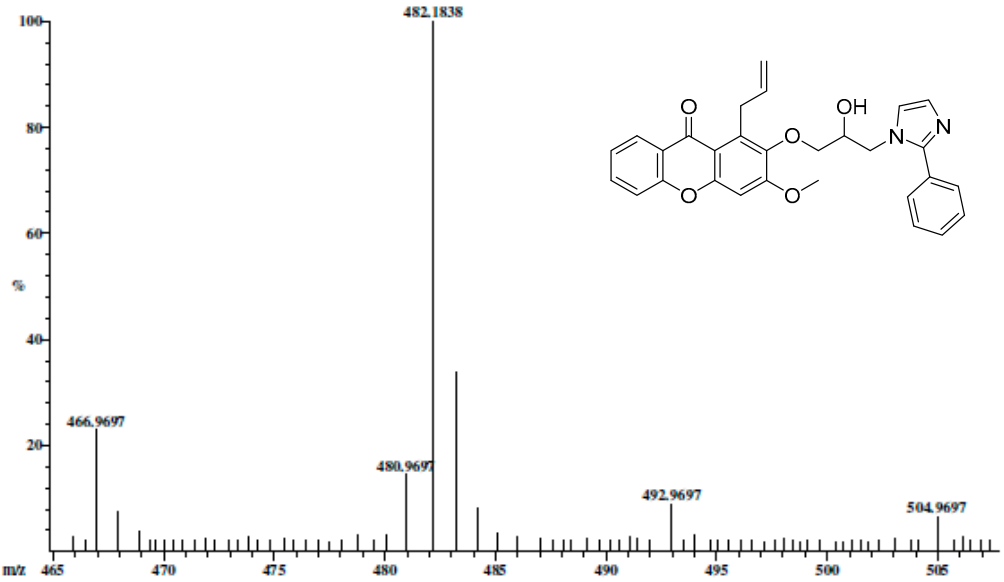


Figure S76. ^{13}C NMR (187.5 MHz, DMSO-d_6) spectrum of **12e**



Selected Isotopes : $H_{0-26}C_{0-29}N_{0-2}O_{0-5}$ **Error Limit : 5 ppm**

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*
482.1838	100.0%	$C_{29}H_{26}N_2O_5$	482.1842	-0.8

Figure S77. HRMS (EI) spectra of compound **12e**.

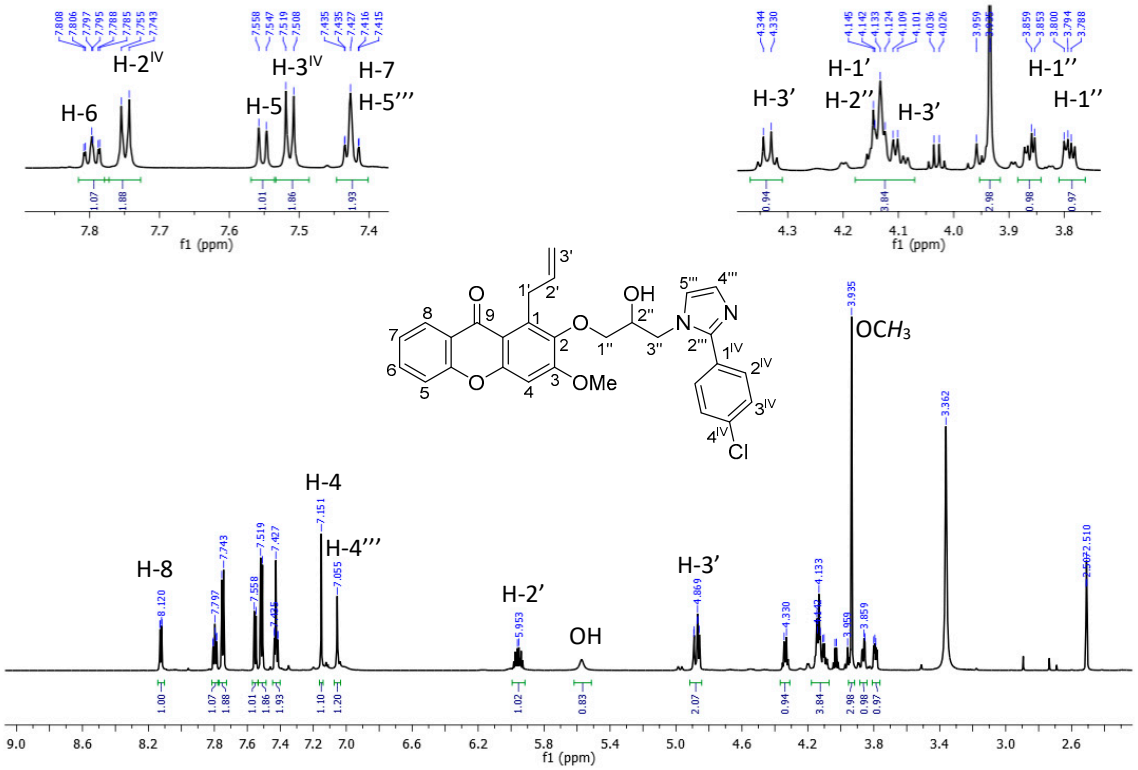


Figure S78. ^{1}H NMR (750 MHz, DMSO-d_6) spectrum of **12f**.

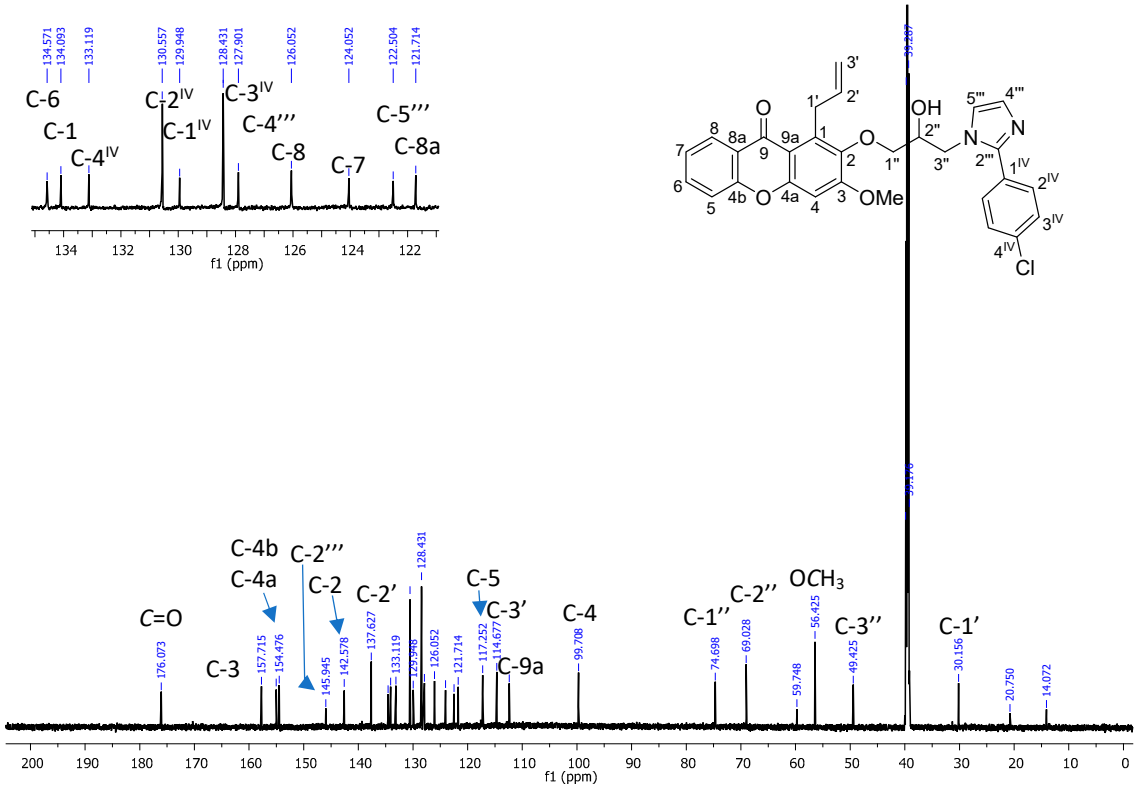
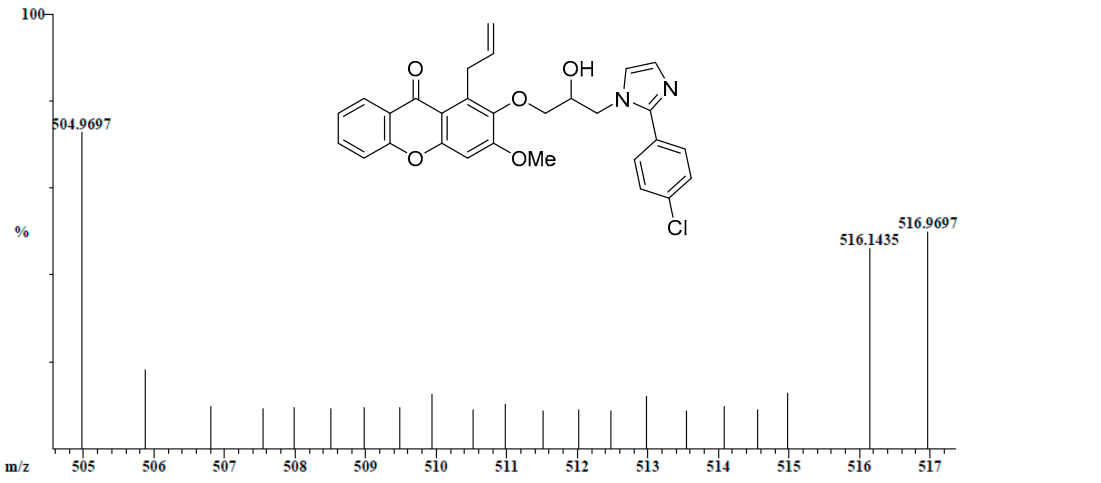


Figure S79. ^{13}C NMR (187.5 MHz, DMSO-d_6) spectrum of **12f**.



Selected Isotopes : $H_{0-25}C_{0-29}N_{0-2}O_{0-5}Cl_{0-1}$ **Error Limit : 5 ppm** **Unsaturation Limits : 0 to 50**

Measured Mass	*% Base*	*Formula*	*Calculated Mass*	*Error*	*Unsaturation*
516.1435	46.1%	$C_{29}H_{25}N_2O_5Cl$	516.1452	-3.3	18.0

Figure S80. HRMS (EI) spectra of compound **12f**.

Table S1. Docking results of **10c** at the active site binding pocket of isomaltase.

Compound	Binding energy Δ*G* (kcal/mol)	Interaction residues	Polar interactions	Hydrophobic interactions
10c	-9.82	Tyr158, Phe159, Phe178, Val216, Gln279, His280, Phe303, Arg315, Tyr316, Asp352, Glu411, Arg442	C-H····O (Tyr316) C-H····O (Glu411) O····H-N (Arg442)	**π-alkyl**-Phe178, Val216 **π-cation**-Arg315 **π-anion**-Asp352

10c

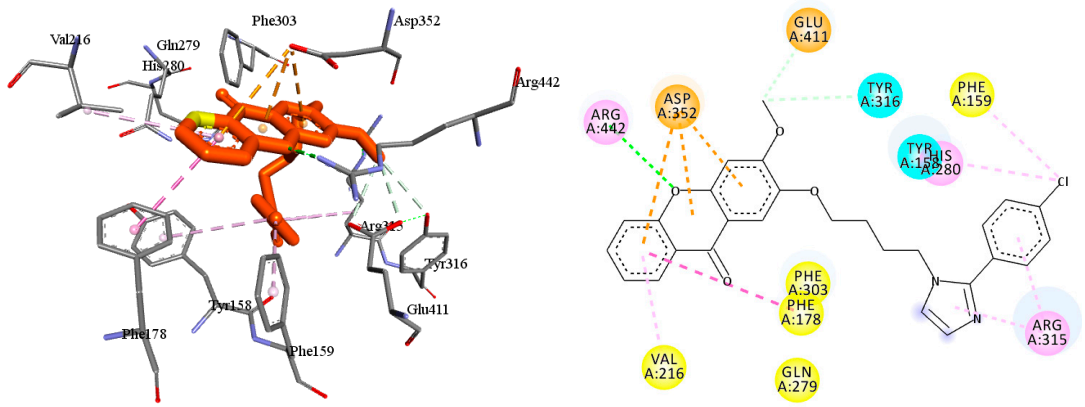
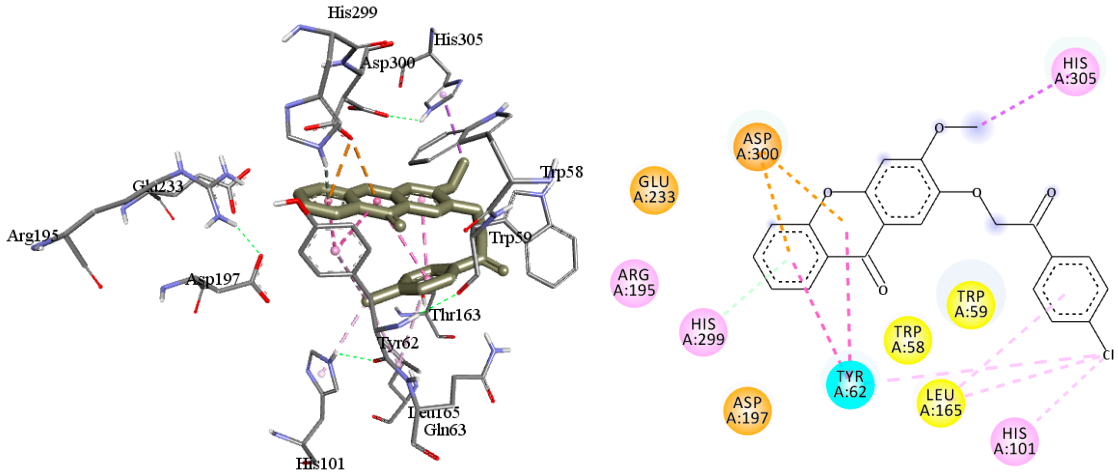


Figure 81. Molecular docking found for **10c** within the active pocket of isomaltase.

Table S2. Docking results of imidazole-substituted xanthones **6c**, **9a** at the active site binding pocket of α-amylase.

Compound	Binding energy Δ*G* (kcal/mol)	Interaction residues	Polar interactions	Hydrophobic interactions
6c	-7.86	Trp58, Trp59, Tyr62, His101, Leu165, Arg195, Asp197, Glu233, His299, Asp300, His305	C-H…...O (His299)	**π-π stacked**-Tyr62 **π-alkyl**-Leu165 **π-anion**-Asp300 **π-sigma**-His305
9a	-6.67	Trp58, Trp59, Tyr62, Leu165, Arg195, Asp197, Glu233, His299, Asp300, His305	C-H…...O (His299)	**π-π T-shaped**-Tyr62 **π-anion**-Asp300 **π-sigma**-His305

6c



9a

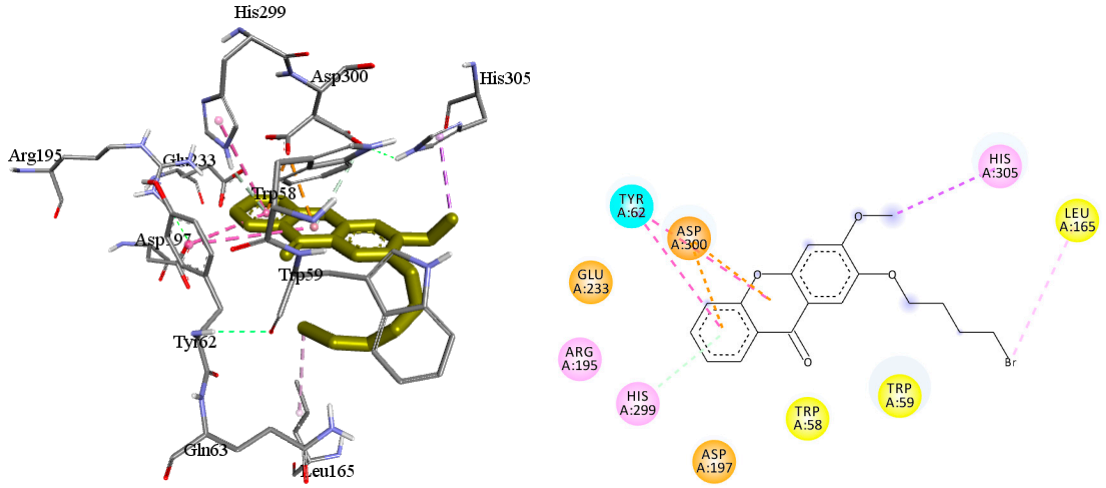


Fig. S82. Molecular docking found for **6c** and **9a** at the active site binding pocket of α-amylase.

Table S3. Calculated physicochemical properties of **1**, **6a**, **6c**, **6e**, **7**, **9a-b**, **10c**, **10f**, **11b**, **12b-f**, and (**14**).

Compound	MW (g/mol)	Log P	Log S	PSA	H-A	H-D
14	645.605	-7.17	0.58	321.17	19	14
1	242.229	2.95	-4.64	55.76	4	1
6a	314.292	2.78	-4.86	71.06	6	0
6c	394.809	4.79	-7.31	61.83	5	0
6e	434.874	5.82	-8.02	61.83	6	0
7	282.294	3.97	-5.36	55.76	4	1
9a	377.233	4.90	-6.34	44.76	4	0
9b	417.298	5.93	-7.05	44.76	4	0
10c	474.943	6.02	-7.79	62.58	6	0
10f	515.007	7.05	-8.51	62.58	6	0
11b	338.358	3.87	-5.82	57.29	5	0
12b	442.470	3.93	-6.39	82.81	7	1
12c	476.915	4.54	-7.13	82.81	7	1
12d	406.437	3.32	-4.96	82.81	7	1
12e	482.534	4.96	-7.10	82.81	7	1
12f	516.980	5.57	-7.84	82.81	7	1

MW, molecular weight (<500 g/mol); *Log P,* octanol/water partition coefficient (<5); *Log S,* aqueous solubility; *PSA,* topological polar surface area; *HA,* hydrogen bond acceptor (<10); *HD,* hydrogen bond donor (<5)

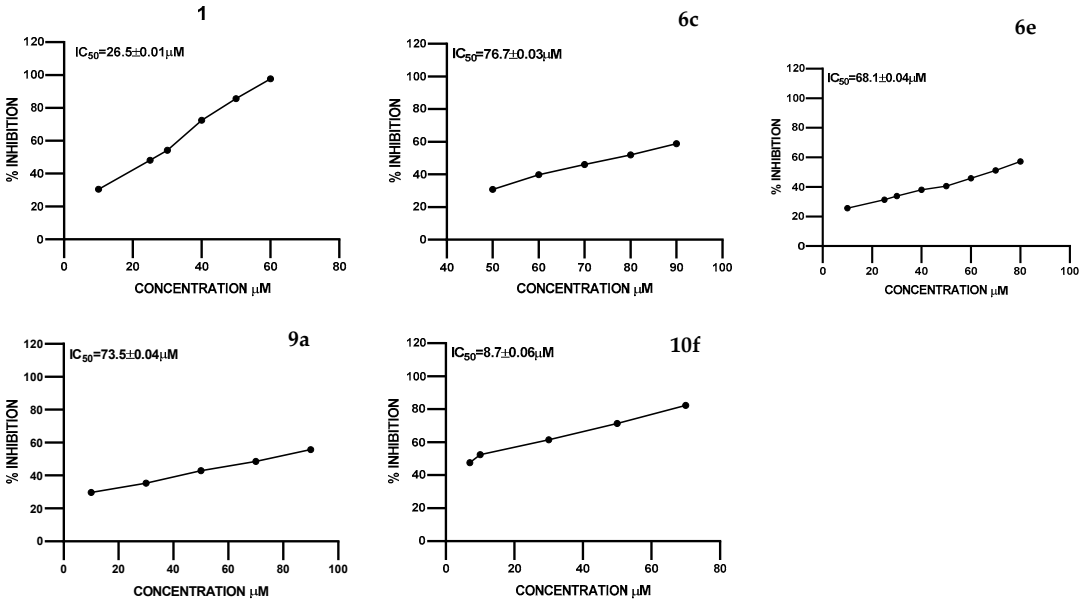


Figure S83. IC_{50} of compounds against α-amylase enzyme.

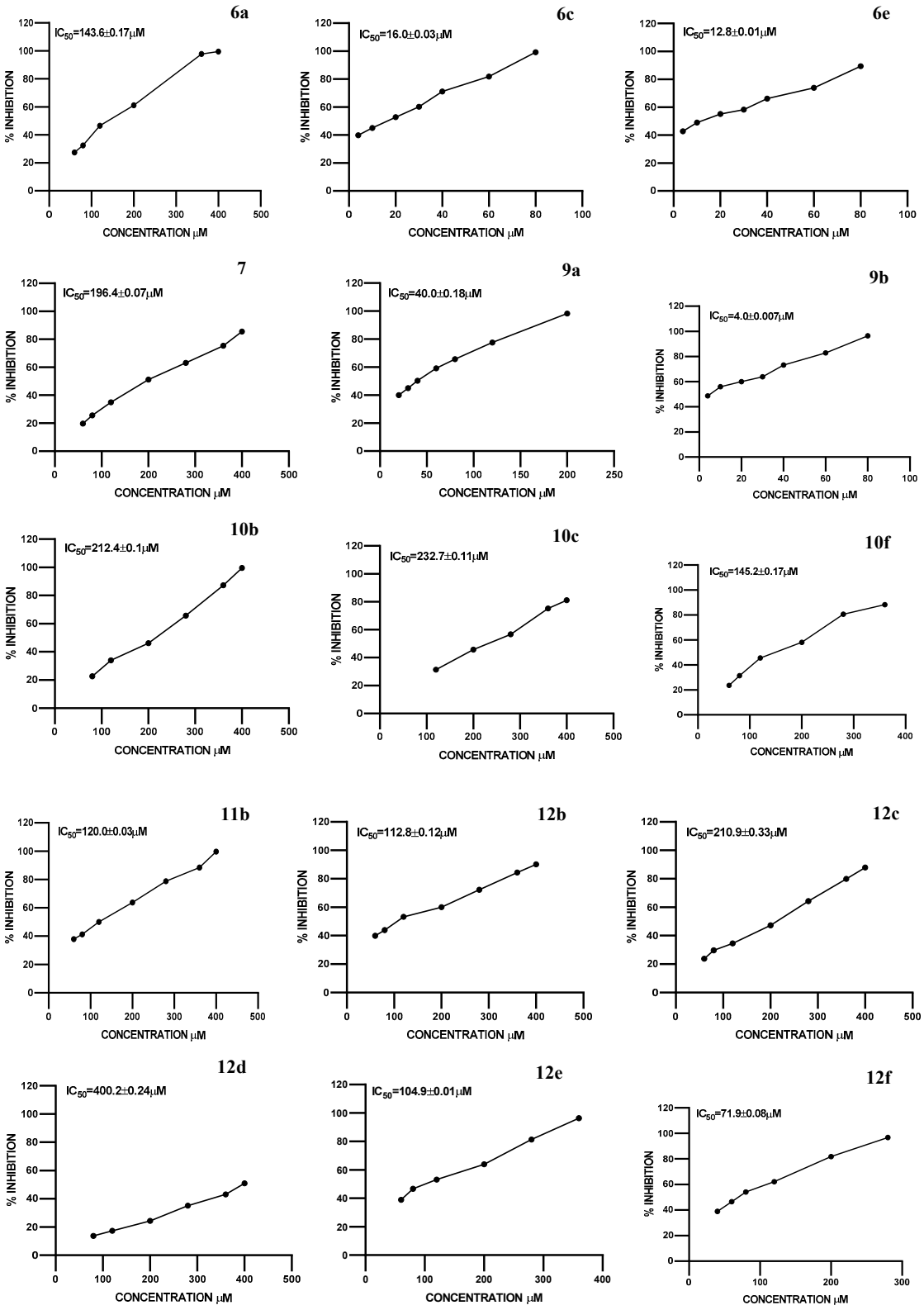


Figure S84. IC_{50} of compounds against α-glucosidase enzyme.